REMARKS

Claim amendments

Original claims 1 - 12 have been examined and stand rejected.

Claims 1 - 4, 6 - 7, 9- 10, and 12 are cancelled herein without prejudice to their further prosecution, or to prosecution of claims of similar scope, in one or more continuation applications.

Claims 13 - 17 are newly added, and claims 5, 8 and 11 amended herein to depend directly or indirectly from one or more of the new claims.

Claims 13 - 17, 5, 8, and 11 are thus presented for further examination.

Support for new claims 13 - 17 can be found throughout the specification as filed, and particularly as follows; no new matter has been added.

Support for treating otitis media with concurrent perforation of the tympanic membrane can be found, *e.g.*, in original claim 7, and in the specification particularly at paragraphs [0005], [0007], [0016], [0021], and elsewhere.

Support for the nonotoxicity of AAT and ilomastat can be found, *inter alia*, in paragraphs [0009] and [0037] and extensively in Example 3, paragraphs [0076] - [0094].

Support for use of recombinant, yeast-expressed, rAAT can be found, *e.g.*, at paragraph [0031].

Support for the administration of a matrix metalloprotease inhibitor, such as ilomastat, as an adjunct to AAT treatment can be found throughout the specification, and particularly in the abstract, paragraphs [0002], [0007], [0035], [0036], [0038], [0039], [0056], [0058], and in the Examples.

Rejections under 35 U.S.C. §102 and § 103

Claims 1 - 4, 6 and 10 have been rejected under 35 U.S.C. § 102(e) as anticipated by Shapiro, U.S. Pat. No. 6,489,308 ("Shapiro"), as further "evidenced by"

Grote *et al.* (U.S. Patent No. 6,670,327) ("Grote"). Claims 5, 7 - 9, 11 and 12 have been rejected under 35 U.S.C. § 103 as having been obvious over Shapiro in view of Grote.

Shapiro proposes to administer alpha 1-antitrypsin (AAT) as a therapy for a variety of disorders, including, *inter alia*, "hot-dog headache", "dysmenorrhea", "HIV infection", "glutamate induced Chinese restaurant syndrome", and "chronic otitis media":

> [s]pecific diseases or disorders for which the therapeutic methods of the invention are beneficial include but are not limited to inflammatory diseases or disorders, hypotension, and the like. The disease or disorder can be selected from the group consisting of but not limited to acquired tubulointerstitial disease, acute pancreatitis, acute respiratory failure, acute respiratory distress syndrome (ARDS), age-associated memory impairment, AIDS, airway inflammation, Alzheimer's disease, amyotrophic lateral sclerosis, asthma, atherosclerosis, autoimmune disease, myocarditis, carcinogenesis, cerebral ischemia, cerebrovascular disease, chronic liver disease, chronic lung disease, chronic obstructive pulmonary disease, chronic otitis media, congestive heart failure, coronary artery disease, coronary artery ectasia, diabetes mellitus, diabetic neuropathy, dysfunctional uterine bleeding, dysmenorrhea, endotoxic shock, end-stage renal disease, falciparum malaria, gastric carcinogenesis, gastrointestinal pathophysiology, glaucoma, glutamate-induced asthma, glutamate induced Chinese restaurant syndrome, heart failure, heat stress, gastritis, `hot-dog headache`, Hirschsprung's disease, HIV infection, hypertension, hypoxemic respiratory failure, inflammatory arthritis, inflammatory bowel disease (Crohn's disease and ulcerative colitis), inflammatory joint diseases, liver cirrhosis, liver disease, Lyme neuroborreliosis, migraine, multiple sclerosis, neonatal and pediatric respiratory failure, nephrotoxicity, neurodegenerative diseases, orthopedic disease, osteoarthritis, oxidant stress, Parkinson's disease, pediatric pulmonary disease, pleural inflammation, preeclampsia, primary ciliary dyskinesia, primary pulmonary hypertension, protozoan infections, pugilistic Alzheimer's disease, pulmonary hypertension, retinal disease, septic shock, sickle cell anemia, rheumatoid arthritis, stroke, systemic lupus erythematosus, traumatic brain injury, tumor progression, or vascular disease. These diseases are thought to be mediated, at least in part, by aberrant levels of nitric oxide. In specific embodiments, the inflammatory disease or disorder is mediated at least in part by an agent selected from the group consisting of γ-interferon and lipopolysaccharide.

> As noted above, the present invention can be used in the treatment of hypotension, including but not limited to hypotension resulting from septic, endotoxic, hypovolemic, or traumatic shock, chronic hypotension, and disorders associated with hypotension, such as priapism.[1]

AAT is administered variously "by injection (*e.g.*, subcutaneous, intramuscular, intravenous, intraarterial, intraperitoneal), by continuous intravenous infusion, transdermally, orally (*e.g.*, tablet, pill, liquid medicine), by implanted osmotic pumps (*e.g.*, Alza Corp.), by suppository or aerosol spray."[2]

Shapiro is not alone in suggesting that AAT might prove efficacious as a therapy in otitis.[3]

For otitis externa -- "swimmer's ear" -- topical therapy with AAT is not implausible: administration to the external ear canal brings AAT into direct contact with the situs of infection and inflammation. For otitis media, however, AAT applied topically to the external acoustic meatus cannot gain access to the middle ear absent perforation of the tympanic membrane. Curiously, and significantly, neither Shapiro nor others who have suggested treating otitis with topical AAT have contemplated the physical barrier posed by an intact tympanic membrane.

In that subset of otitis media cases presenting with perforated tympanic membrane, AAT applied topically to the external canal can readily gain access to the middle ear, and thus to the site of infection and inflammation. In these cases, however, the potential toxicity of therapeutic agents is a critical clinical concern. *See*, *e.g.*, Roland *et al.*, "Animal ototoxicity of topical antibiotics and the relevance to clinical treatment of human subjects," *Otolaryngol. Head Neck Surg.* 130:S57-S78 (2004) and Matz *et al.*,

---

[1] Shapiro, col. 13, line 33 - col. 14, line 8.

[2] Shapiro, col. 17, lines 34- 38.

[3] See, for example, U.S. Patent No. 6,174,859, previously made of record.

"Ototoxicity of ototopical antibiotic drops in humans," *Otolaryngol. Head Neck Surg.* 130:S79-S82 (2004), enclosed herewith.

Claim 13, now the sole independent claim, is drawn with particularity to treatment of otitis media presenting with perforated tympanic membrane, using effective, yet nonototoxic, amounts of AAT:

> 13 (new). A method of treating an individual having otitis media and a perforated tympanic membrane, the method comprising:
>
> administering an effective, nonototoxic, amount of recombinant alpha one-antitrypsin (AAT) to the middle ear by topical application to the external auditory canal.

Shapiro neither discloses the selection for treatment of that subset of otitis media cases presenting with perforated tympanic membranes, nor that a topical dose[4] may be found in such cases that is both effective and nonototoxic. Nor could he: applicants were the first to demonstrate that topical AAT and topical ilomastat are nonototoxic.

Lacking elements of applicants' claim 13, Shapiro cannot anticipate claim 13 or claims that depend directly or indirectly therefrom.

Claim 15, newly added by amendment herein, further requires the administration of an effective, nonototoxic, amount of an inhibitor of at least one species of matrix metalloprotease (MMP), with claim 16 drawn with particularity to administration of ilomastat and claim 17 specifying that rAAT be commonly composited therewith.

Shapiro is silent as to the use of matrix metalloprotease inhibitors, such as ilomastat, as an adjunct to AAT treatment in otitis, and for this additional reason cannot anticipate claims 15, 16 and 17 and claims that depend therefrom.

---

[4] Presuming Shapiro's "aerosol spray" to intend topical delivery.

Claim 8, which depends multiply from claims 13 - 17, further stratifies the patient population, specifically claiming topical therapy in cases in which the tympanic membrane perforation is caused by tympanostomy.[5] Claim 11, which depends from claim 8, further selects for treatment that subset of post-tympanostomy cases exhibiting acute post-tympanostomy otorrhea.

Shapiro makes no mention of post-tympanostomy otitis,[6] nor of the subset thereof that exhibits acute post-tympanostomy otorrhea, and for this additional reason cannot vitiate the novelty of claim 8 or claims that depend therefrom.

All pending claims, as newly added or amended herein, are novel over Shapiro, as evidenced by Grote. Applicants thus respectfully submit that the rejection under 35 U.S.C. § 102(e), having been obviated, should be withdrawn.

In rejecting claims 5, 7 - 9, 11 and 12 as having been obvious, the Examiner acknowledges that "Shapiro does not teach specific conditions such as a perforated tympanic membrane," but notes that "Grote . . . teach[es] that . . . tympanic membrane perforation . . . [is] associated with otitis media."[7] On this basis, the Examiner suggests that "[i]t would have been obvious . . . to modify the teaching of Shapiro to employ alpha one-antitrypsin for the treatment of chronic otitis media in human[s] suffering from a perforated tympanic membrane. . . ."[8]

Applicants respectfully disagree.

---

[5] Tympanostomy is typically performed to insert tympanostomy tubes, intended to equalize pressure across the tympanic membrane.

[6] In such cases, "otitis" may largely reflect surgery-induced inflammation on a background of chronic otic inflammation, rather than a reaction to acute bacterial infection.

[7] Office action, paragraph bridging pages 3 - 4.

[8] Office action, page 4.

Prior to applicants' discovery, it could not be predicted whether AAT -- or inhibitors of matrix metalloproteases, notably ilomastat, or ilomastat in combination with AAT -- would prove sufficiently nonototoxic as to permit effective topical administration in the setting of a perforated tympanic membrane. Indeed, with agents drawn from a wide range of chemical classes having already, in some cases tragically, proven ototoxic,[9] the art instead clearly counsels caution in attempting topical therapy with novel agents. Given such caution, the cited art could not have provided a reasonable expectation that an effective, yet nonototoxic, dose of AAT or ilomastat could found that would permit successful treatment of otitis media in the setting of perforated tympanic membrane. The Examiner's *prima facie* case of obviousness is, therefore, critically infirm. *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) ("The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art.").

With failure of the *prima facie* case, the burden of production has not properly been shifted to applicants, and applicants are entitled, without more, to their claims. *In re Oetiker*, 977 F.2d 1443 (Fed. Cir. 1992).

Furthermore, applicants respectfully submit that the ototoxicity art clearly teaches away from the use of novel compounds as topical agents, a secondary indicium of the nonobviousness of applicants' topical administration of antiprotease in the clinical context of perforate tympanic membranes.

Applicants respectfully submit that the claims as now pending would have been nonobvious over the art of record, and that the rejection is in error and should be withdrawn.

---

[9] See Roland *et al.*, Table 1.

CONCLUSION

Applicants submit that the present application is in condition for allowance, and respectfully request the same. If the Examiner believes that any matters remain outstanding prior to passing this case to issue, however, applicants respectfully request that the Examiner call the undersigned attorney, newly of record, for a telephonic interview.

Respectfully submitted,

HELLER EHRMAN WHITE & MCAULIFFE LLP

Date: APRIL 6, 2005

Daniel M. Becker, M.D. (Reg. No. 38,376)
Attorney for Applicant

275 Middlefield Road
Menlo Park, CA 94025
(650) 324-7000
(650) 324-6665 (FAX)
Customer No. 25213

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/007,215	09/22/2004	6174859	39042.0005	9354

7590 11/22/2004

EXAMINER	
ART UNIT	PAPER NUMBER

John Lezdey
John Lezdey & Associates
1409 N. Ft. Harrison
Suite A
Clearwater, FL 33755

DATE MAILED: 11/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Order Granting / Denying Request For Ex Parte Reexamination	Control No.	Patent Under Reexamination	
	90/007,215	6174859	
	Examiner	Art Unit	
	Phyllis G. Spivack	1614	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

The request for *ex parte* reexamination filed *22 September 2004* has been considered and a determination has been made. An identification of the claims, the references relied upon, and the rationale supporting the determination are attached.

Attachments: a)☐ PTO-892, b)☒ PTO-1449, c)☐ Other: _____

1. ☒ The request for *ex parte* reexamination is GRANTED.

RESPONSE TIMES ARE SET AS FOLLOWS:

For Patent Owner's Statement (Optional): TWO MONTHS from the mailing date of this communication (37 CFR 1.530 (b)). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).**

For Requester's Reply (optional): TWO MONTHS from the **date of service** of any timely filed Patent Owner's Statement (37 CFR 1.535). **NO EXTENSION OF THIS TIME PERIOD IS PERMITTED.** If Patent Owner does not file a timely statement under 37 CFR 1.530(b), then no reply by requester is permitted.

2. ☐ The request for *ex parte* reexamination is DENIED.

This decision is not appealable (35 U.S.C. 303(c)). Requester may seek review by petition to the Commissioner under 37 CFR 1.181 within ONE MONTH from the mailing date of this communication (37 CFR 1.515(c)). **EXTENSION OF TIME TO FILE SUCH A PETITION UNDER 37 CFR 1.181 ARE AVAILABLE ONLY BY PETITION TO SUSPEND OR WAIVE THE REGULATIONS UNDER 37 CFR 1.183.**

In due course, a refund under 37 CFR 1.26 (c) will be made to requester:

a) ☐ by Treasury check or,

b) ☐ by credit to Deposit Account No. _____, or

c) ☐ by credit to a credit card account, unless otherwise notified (35 U.S.C. 303(c)).

Phyllis Spivack

PHYLLIS SPIVACK
PRIMARY EXAM

Phyllis G. Spivack
Primary Examiner
Art Unit: 1614

cc:Requester (if third party requester)

Decision on Request for Reexamination

A substantial new question of patentability affecting claims 1-10, 12-14 and 16 of United States Patent Number 6,174,859 is raised by the request for reexamination filed September 22, 2004. For the reasons given below, the Examiner finds new questions of patentability affecting claims 1-10, 12-14 and 16 and the request for *ex parte* reexamination pursuant to 37 CFR 1.510 is GRANTED.

Extensions of time under 37 CFR 1.136(a) will not be permitted in these proceedings because the provisions of 37 CFR apply only to "an applicant" and not to parties in a reexamination proceeding. Additionally, 35 U.S.C. 305 requires that reexamination proceedings "will be conducted with special dispatch" (37 CFR 1.550(a)). Extension of time in reexamination proceedings are provided for in 37 CFR 1.550(c).

Claims Considered Unpatentable by Requester

1) The Requester considers claims 1, 2, 5, 7, 9, 10 and 16 to be anticipated under various subsections of 35 U.S.C. 102 by Lezdey et al., U.S. Patent 5,217,951, and under 35 U.S.C. 103 as being obvious thereover, either alone or in view of Avidano et al., Otolaryngology – Head and Neck Surgery.

2) The Requester considers claims 1, 5, 9 and 16 to be anticipated under various subsections of 35 U.S.C. 102, and obvious under 35 U.S.C. 103, over Lezdey et al., U.S. Patent 5,290,762.

3) The Requester considers claims 1, 2, 9, 10 and 16 to be anticipated under various subsections of 35 U.S.C. 102, and obvious under 35 U.S.C. 103, over Lezdey et al., U.S. Patent 5,008,242.

4) The Requester considers claims 3 and 12 to be obvious under 35 U.S.C. 103 over Lezdey et al., U.S. Patent 5,008,242.

5) The Requester considers claims 3, 7, 8, 12 and 13 to be obvious under 35 U.S.C. 103 over either or both of Lezdey et al., U.S. Patent 5,008,242, and Lezdey et al., U.S. Patent 5,217,951, in view of Avidano et al., Otolaryngology – Head and Neck Surgery.

6) The Requester considers claim 6 to be obvious under 35 U.S.C. 103 over either or both of Lezdey et al., U.S. Patent 5,217,951, and Lezdey et al., U.S. Patent 5,290,762, in view of either or both of Lezdey et al., U.S. Patent 5,190,917, and Lezdey et al., U.S. Patent 5,215,965.

7) The Requester considers claim 6 to be obvious under 35 U.S.C. 103 over either or both of Lezdey et al., U.S. Patent 5,217,951, and Lezdey et al., U.S. Patent 5,290,762,

in view of any one or more of U.S. Patents 5,061,729; 5,679,665; 4;474,751; 5631,241; or; 4,025,620.

8) The Requester considers claims 4 and 14 to be obvious under 35 U.S.C. 103 over either or both of Forney et al., J. Eukaryot. Microbiol., and Forney et al., Antimicrobial Agents Chemother., in view of any one or more of Lezdey et al., U.S. Patents 5,217,951; 5,290,762; and 5,008,242.

Decision on Request

It is agreed that consideration of Lezdey et al., U.S. Patent 5,217,951, raises a substantial new question of patentability because the reference teaches the treatment of an otic infection with a composition comprising PROLASTIN, a sterile preparation of α_1-antitrypsin, of which kallikrein and kinin inhibition is an inherent property.

It is agreed consideration of Lezdey et al., U.S. Patent 5,290,762, raises a substantial new question of patentability because the reference teaches or suggests various limitations of the present claims.

It is agreed consideration of Lezdey et al., U.S. Patent 5,008,242, raises a substantial new question of patentability because the reference teaches treatment of optic and otic inflammation using alpha-1-antitrypsin in combination.

It is agreed consideration of Lezdey et al., U.S. Patent 5,008,242, raises a substantial new question of patentability because the reference teaches the administration of alpha-1-antitrypsin in the treatment of 'swimmer's ear', otitis externa. The condition is often caused by *pseudomonas aeruginosa*.

It is agreed consideration of Lezdey et al., U.S. Patent 5,008,242, Lezdey et al., U.S. Patent 5,217,951, and Avidano et al., Otolaryngology – Head and Neck Surgery, raises a substantial new question of patentability for the points set forth *supra*. Avidano provides a reasonable expectation that treatment will be successful.

It is agreed consideration of Lezdey et al., U.S. Patent 5,190,917, and Lezdey et al., U.S. Patent 5,215,965, raises a substantial new question of patentability because both documents teach the administration of corticosteroids in admixture or in conjunction with serine protease inhibitors, of which alpha-1-antitrypsin is an example.

It is agreed consideration of U.S. Patents 5,061,729; 5,679,665; 4;474,751; 5631,241; or, 4,025,620, raises a substantial new question of patentability because these documents teach the administration of corticosteroids for use in therapeutic compositions intended for otic and/or ophthalmic administration.

It is agreed consideration of Forney et al., J. Eukaryot. Microbiol., Forney et al., Antimicrobial Agents Chemother. raises a substantial new question of patentability because Forney teaches the anticryptosporidial potential of alpha-1-antitrypsin. Cryptosporidium parvum is a parasite within the scope of instant claim 14.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phyllis G. Spivack whose telephone number is 571-272-0585. The examiner can normally be reached from Monday to Friday from 9:30 to 6 PM.

If attempts to reach the Examiner by telephone are unsuccessful after one business day, the Examiner's supervisor, Chris Low, can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phyllis Spivack

Phyllis G. Spivack
Primary Examiner
Art Unit 1614

November 17, 2004

PHYLLIS SPIVACK
PRIMARY EXAMINER

Ex Parte REEXAMINATION INFORMATION DISCLOSURE STATEMENT PTO-1449	PATENT NO.: 6,174,859	ISSUED: January 16, 2001
	REEXAM REQUEST CONTROL NO.: 90/007215	

U.S. PATENT DOCUMENTS

EXAMINER'S INITIALS	CITE NO.	PATENT NO.	ISSUE DATE mm-dd-yyy	NAME	FILING DATE	RELEVANT PAGES, FIGS.
PS		5,780,440	07-14-1998	Lezdey *et al.*	10-11-1996	
PS		5,532,215	07-02-1996	Lezdey *et al.*	10-03-1994	
PS		5,492,889	02-20-1996	Lezdey *et al.*	10-17-1994	
PS		5,346,886	09-13-1994	Lezdey *et al.*	11-15-1993	
PS		5,290,762	03-01-1994	Lezdey *et al.*	02-17-1993	
PS		5,217,951	06-08-1993	Lezdey *et al.*	10-18-1991	
PS		5,215,965	06-01-1993	Lezdey *et al.*	09-05-1991	
PS		5,190,917	03-02-1993	Lezdey et al	04-11-1991	
PS		5,166,134	11-24-1992	Lezdey *et al.*	06-04-1991	
PS		5,134,119	07-28-1992	Lezdey *et al.*	01-18-1991	
PS		5,114,917	05-19-1992	Lezdey *et al.*	10-02-1990	
PS		5,093,316	03-03-1992	Lezdey *et al.*	10-02-1990	
PS		5,008,242	04-16-1991	Lezdey *et al.*	12-04-1989	
PS		5,679,665	10-21-1997	Bergamini *et al.*	10-27-1995	
PS		5,631,241	05-20-1997	della Valle *et al.*	04-21-1995	
PS		5,061,729	10-29-1991	Kinoses *et al.*	06-08-1988	
PS		4,474,751	10-02-1984	Haslam *et al.*	05-16-1983	
PS		4,025,620	05-24-1977	Beyer *et al.*	10-22-1975	

Phyllis Spivack 11/17/04

[redacted]

Ex Parte REEXAMINATION	PATENT NO.: 6,174,859	ISSUED: January 16, 2001
INFORMATION DISCLOSURE STATEMENT	REEXAM REQUEST CONTROL NO.: 90/007215	
PTO-1449		

FOREIGN PATENT DOCUMENTS

EXAMINER'S INITIALS	CITE NO.	PATENT NO.	COUNTRY	DATE		TRANSLATION YES	TRANSLATION NO

NONPATENT LITERATURE DOCUMENTS

EXAMINER'S INITIALS	CITE NO.	AUTHOR, Title, Date	
PS		AVIDANO *et al.*, "Analysis of protease activity in human otitis media," *Otolaryngology - Head and Neck Surgery*, 119(4):246 - 351 (October 1998).	
PS		BAYER CORPORATION. Alpha1-Proteinase Inhibitor (Human). Prolastin®. Revised March 2003.	
		~~CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC). "Swimmer's Ear" (Otitis Externa). Fact Sheet for Swimmers. Date unknown.~~	
PS		COAN *et al.*, "Preparation and Properties of Alpha$_1$-Proteinase Inhibitor Concentrate from Human Plasma," *Vox. Sang.* 48:333-342 (1985).	
PS		FORNEY *et al.*, "Anticryptosporidial potential of alpha-1-antitrypsin," *J. Eukaryot. Microbiol.* 43(5):63S (Sept-Oct 1996).	

Phyllis Spinack 11/17/04

[redacted]

Ex Parte REEXAMINATION INFORMATION DISCLOSURE STATEMENT PTO-1449	PATENT NO.: 6,174,859	ISSUED: January 16, 2001
	REEXAM REQUEST CONTROL NO.: 90/007,215	

PS		FORNEY *et al.*, "Synergistic anticryptosporidial potential of the combination of alpha-1-antitrypsin and paromomycin," *Antimicrobial Agents Chemother.*, Sept. 1997, p. 2006 - 2008	

EXAMINER P. SWIGER DATE CONSIDERED 11/18/04

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant

SV 2060994 v1
9/6/04 11:03 AM (39042.0005)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re:	Patent No. 6,174,859	Examiner:	Spivack
Re-Examination Control No.:	90/007215	Art Group:	1614

Patent Owner's Statement

Patent owner will file a Declaration swearing back of the publication date of the Avidano et al article.

Also, Patent owner will submit scientific publications which illustrate that there is a distinction in treating bacterial diseases from mast cell or viral disease.

Respectfully submitted,

John Lezdey
Attorney for Patent Owner

4625 East Bay Drive
Suite 302
Clearwater, FL 33764
Phone: (727) 539-0633
Fax: (727) 539-7241

PTO/SB/57 (04-04)
Approved for use through 04/30/2007. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also referred to as FORM PTO-1465)

REQUEST FOR *EX PARTE* REEXAMINATION TRANSMITTAL FORM

Address to:
Mail Stop *Ex Parte* Reexam
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Attorney Docket No.: 39042.0005

Date: 22 SEPT 2004

1. ☑ This is a request for *ex parte* reexamination pursuant to 37 CFR 1.510 of patent number 6,174,859 issued January 16, 2001. The request is made by:

   ☐ patent owner. ☑ third party requester.

2. ☑ The name and address of the person requesting reexamination is:

   Ginger R. Dreger & Daniel M. Becker
   Heller Ehrman White & McCauliffe, LLP
   275 Middlefield Road, Menlo Park, CA 94025

3. ☐ a. A check in the amount of $_____ is enclosed to cover the reexamination fee, 37 CFR 1.20(c)(1);

   ☑ b. The Director is hereby authorized to charge the fee as set forth in 37 CFR 1.20(c)(1) to Deposit Account No. 08-1641 (39042.0005) (submit duplicate of this form for fee processing); or

   ☐ c. Payment by credit card. Form PTO-2038 is attached.

4. ☑ Any refund should be made by ☐ check or ☑ credit to Deposit Account No. 08-1641 37 CFR 1.26(c). If payment is made by credit card, refund must be to credit card account.

5. ☑ A copy of the patent to be reexamined having a double column format on one side of a separate paper is enclosed. 37 CFR 1.510(b)(4)

6. ☐ CD-ROM or CD-R in duplicate, Computer Program (Appendix) or large table

7. ☐ Nucleotide and/or Amino Acid Sequence Submission
   If applicable, all of the following are necessary.

   a. ☐ Computer Readable Form (CRF)
   b. Specification Sequence Listing on:

      i. ☐ CD-ROM (2 copies) or CD-R (2 copies); **or**
      ii. ☐ paper

   c. ☐ Statements verifying identity of above copies

8. ☐ A copy of any disclaimer, certificate of correction or reexamination certificate issued in the patent is included.

9. ☑ Reexamination of claim(s) 1,2,3,4,5,6,7,8,9,10,12,13,14 and 16 is requested.

10. ☑ A copy of every patent or printed publication relied upon is submitted herewith including a listing thereof on Form PTO-1449 or equivalent.

11. ☐ An English language translation of all necessary and pertinent non-English language patents and/or printed publications is included.

10/05/2004 HTUITTY 00000002 081641 90007215

Express Mail: EL 976 544 109 US
Date Mailed: 22 September 2004

[redacted]

12. ☑ The attached detailed request includes at least the following items:

a. A statement identifying each substantial new question of patentability based on prior patents and printed publications. 37 CFR 1.510(b)(1)
b. An identification of every claim for which reexamination is requested, and a detailed explanation of the pertinency and manner of applying the cited art to every claim for which reexamination is requested. 37 CFR 1.510(b)(2)

13. ☐ A proposed amendment is included (only where the patent owner is the requester). 37 CFR 1.510(e)

14. ☑ a. It is certified that a copy of this request (if filed by other than the patent owner) has been served in its entirety on the patent owner as provided in 37 CFR 1.33(c).
The name and address of the party served and the date of service are:

John LEZDEY (Reg. No. 22,735)
4625 E Bay Dr, Ste 302
Clearwater, FL 33764

by deposit in first class mail with adequate postage, 37 CFR 1.248(a)(4).

Date of Service: 22 SEPTEMBER 2004 ; or

☐ b. A duplicate copy is enclosed since service on patent owner was not possible.

15. Correspondence Address: Direct all communication about the reexamination to:

☑ Customer Number: 25213

OR

☐ Firm or Individual Name					
Address (line 1)					
Address (line 2)					
City		State		Zip	
Country					
Telephone		Fax			

16. ☑ The patent is currently the subject of the following concurrent proceeding(s):
☐ a. Copending reissue Application No. _____
☐ b. Copending reexamination Control No. _____
☐ c. Copending Interference No. _____
☑ d. Copending litigation styled:

Alphamed Pharmaceuticals Corp. v. Arriva Pharmaceuticals, Inc.
United States District Court, Southern District of Florida
Case No. 03-20078 CIV Altonaga/Bandstra

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

[signature] *Authorized Signature*

September 22, 2004 *Date*

Ginger R. Dreger *Typed/Printed Name*

33,055 *Registration No., if applicable*

☐ *For Patent Owner Requester*
☑ *For Third Party Requester*

Requester's Docket No. : 39042.0005

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent No.:	**6,174,859**		
Issued:	June 16, 2001	By Examiner:	Zoreh Fay
From application:	09/286,740	Group Art Unit.:	1614
Filed:	April 6, 1999		
By:	John LEZDEY *et al.*		
For:	METHOD OF TREATMENT		

EL976544109US

Mail Stop *Ex Parte* Reexam
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

THIRD PARTY REQUEST FOR *EX PARTE* REEXAMINATION

Sir:

The undersigned third party respectfully requests *ex parte* reexamination of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14 and 16 of U.S. Patent No. 6,174,859.

In addition to the items identified on the accompanying transmittal, Form PTO-1465, we submit herewith:

- a copy of the single reference considered during prosecution, MPEP § 2218;
- a copy of the patent infringement count of the Second Amended Complaint in the identified litigation, MPEP § 2219; and
- for convenience of the Office, a copy of the instant paper on CD-R.

I. Statement Identifying Each Substantial New Question of Patentability, 37 C.F.R. § 1.510(b)(1)

A. Claims 1, 2, 5, 7, 9, 10 and 16 are anticipated under 35 U.S.C. §§ 102(a), 102(b) and 102(e) by Lezdey *et al.*, U.S. Pat. No. 5,217,951, not previously made of record, and under 35 U.S.C. § 103 would have been obvious thereover, either alone or in view of Avidano *et al.*, "Analysis of protease activity in human otitis media," *Otolaryngology - Head and Neck Surgery*, 119(4):246 - 351, which has not previously been made of record.

B. Claims 1, 5, 9 and 16 are anticipated under 35 U.S.C. §§ 102(a), 102(b), and 102(e) by, and under 35 U.S.C. § 103 would have been obvious over, Lezdey *et al.*, U.S. Pat. No. 5,290,762, not previously made of record.

C. Claims 1, 2, 9, 10 and 16 are anticipated under 35 U.S.C. §§ 102(a), 102(b) and 102(e) by, and under 35 U.S.C. § 103 would have been obvious over, Lezdey *et al.*, U.S. Pat. No. 5,008,242, not previously made of record.

D. Claims 3 and 12 would have been obvious under 35 U.S.C. § 103 over Lezdey *et al.*, U.S. Pat. No. 5,008,242, not previously made of record.

E. Claims 3, 7, 8, 12 and 13 would have been obvious under 35 U.S.C. § 103 over either or both of Lezdey *et al.*, U.S. Pat. No. 5,008,242 and Lezdey *et al.*, U.S. Pat. No. 5,217,951, in view of Avidano *et al.*, "Analysis of protease activity in human otitis media," *Otolaryngology - Head and Neck Surgery*, 119(4):246 - 351, none of which have previously been made of record.

F. Claim 6 would have been obvious under 35 U.S.C. § 103 over either or both of Lezdey *et al.*, U.S. Pat. No. 5,217,951 and Lezdey *et al.*, U.S. Pat. No. 5,290,762 in view of either or both of Lezdey *et al.*, U.S. Pat. No. 5,190,917 and Lezdey *et al.*, U.S. Pat. No. 5,215,965, none of which have previously been made of record.

G. Claim 6 would have been obvious under 35 U.S.C. § 103 over either or both of Lezdey *et al.*, U.S. Pat. No. 5,217,951 and Lezdey *et al.*, U.S. Pat.

No. 5,290,762 in view of any one or more of U.S. Pat. Nos. 5,061,729; 5,679,665; 4,474,751; 5,631,241; or 4,025,620, none of which have previously been made of record.

H. Claims 4 and 14 would have been obvious under 35 U.S.C. § 103 over either or both of Forney *et al.*, "Anticryptosporidial potential of alpha-1-antitrypsin," *J. Eukaryot. Microbiol.* 43(5):63S and Forney *et al.*, "Synergistic anticryptosporidial potential of the combination of alpha-1-antitrypsin and paromomycin," *Antimicrobial Agents Chemother.*, Sept. 1997, p. 2006 - 2008 in view of any one or more of Lezdey *et al.* U.S. Pat. Nos. 5,217,951; 5,290,762; and 5,008,242, none of which have previously been made of record.

[redacted]

II. Identification of Claims and Detailed Explanation, 37 C.F.R. § 1.510(b)(2)

A. Claims 1, 2, 5, 7, 9, 10 and 16 are anticipated under 35 U.S.C. §§ 102(a), 102(b) and 102(e) by Lezdey *et al.*, U.S. Pat. No. 5,217,951, not previously made of record, and under 35 U.S.C. § 103 would have been obvious thereover, either alone or in view of Avidano *et al.*, "Analysis of protease activity in human otitis media," *Otolaryngology - Head and Neck Surgery*, 119(4):246 - 351, which was not previously made of record.

Claims 1, 2, 5, 7, 9, 10 and 16 of the patent for which reexamination is here requested ("the instant patent") are anticipated under 35 U.S.C. §§ 102(a), 102(b) and § 102(e) by Lezdey *et al.*, U.S. Pat. No. 5,217,951, issued June 8, 1993 ("the '951 patent"). The '951 patent, of which the inventor-prosecuting attorney of the instant patent is both an inventor and the prosecuting attorney, was not made of record during prosecution of the instant patent.[1]

Claim 1 is independent; claims 2, 5, 7, 9 and 10 depend directly therefrom. Claim 1 recites as follows:

> 1. A method for treating optic and otic infections, inflammation and kalligrein activity by parasites and microbes which comprises administering to the site of the infection an effective amount of a protease inhibitor selected from the group consisting of alpha 1-antitrypsin, secretory leucocyte protease inhibitor, anti-plasmin inhibitor and a combination thereof in a suitable pharmaceutically acceptable carrier.

---

[1] The applicants filed no Information Disclosure Statement during prosecution of the instant patent; the Examiner cited and applied a single reference, U.S. Pat. No. 5,604,201, a copy of which is enclosed with this Request.

The '951 patent exemplifies the treatment of otic infection with a composition comprising PROLASTIN,[2] a sterile preparation of α_1-antitrypsin (hereinafter, "AAT") prepared from pooled human plasma of normal donors.[3]

PROLASTIN also comprises small amounts of serine protease inhibitors additional to AAT, including α_1-antichymotrypsin (hereinafter, "AAC") and α-2 plasmin inhibitor.[4,5]

Claim 1 of the instant patent reads on administration of such compositions.

Claim 1 employs the open transition phrase, "which comprises." This transitional phrase is "inclusive or open-ended and does not exclude additional, unrecited elements or method steps." MPEP. § 2111.03, citing, *inter alia*, to *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 66 USPQ 2d 1631 (Fed. Cir. 2003); *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 42 USPQ 2d 1608 (Fed. Cir. 1997); and *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts"). Claim 1 thus permits of, and reads on, the administration of agents additional to the protease inhibitors set forth with specificity in the claim's Markush group.

---

2. '951 Example III, col. 6, particularly at lines 33 - 35.

3 See "Alpha1-Proteinase Inhibitor (Human)" Prolastin® product insert, listed on the enclosed form PTO-1449 and submitted herewith.

4 Although the '951 patent states that PROLASTIN "compris[es] about 70% α-1-antitrypsin and about 10 - 18% α-1-antichymotrypsin," '951 col. 6, lines 24 - 25, the product in fact contains 25.0 mg/ml AAT and only 1.5 mg/ml AAC, for an AAT to AAC ratio of approximately 16:1. See Coan *et al.*, *Vox. Sang.* 48:333-342 (1985), referenced in the PROLASTIN product insert, filed herewith.

5 It should be noted in passing that α2-plasmin inhibitor, present as a minor component of PROLASTIN, is itself one of the three species of protease inhibitor recited in claim 1, although the '951 patent does not make clear whether this minor component is present in an amount that is itself effective to treat otic infection.

[redacted]

Such a construction is also clearly mandated by the dependencies from claim 1. Any construction of claim 1 that would serve to exclude the presence of further agents would render each of dependent claims 5, 6, 7, 8, and 11 internally contradictory: these claims, which depend directly or indirectly from claim 1, and thus include all of its limitations, 37 C.F.R. § 1.75(c), are drawn respectively to the further administration of a steroid (claim 5), to the further administration of any one or more of dexamethasone, betametasone, and triamcinolone acetonide (claim 6), to the further administration of an antibiotic (claim 7), to the further administration of an anti-"pseudomonasis" antibiotic (claim 8), and to the further administration of hyaluronic acid (claim 11).

Claim 1 reads on the administration of agents additional to the three protease inhibitor species listed in its Markush group, and thus reads directly upon the '951 patent's exemplary administration of PROLASTIN to treat otic infection.

More generally, the '951 patent both teaches and claims "[a] method for the prophylaxis or direct treatment of non-bronchial mast cell implicated disease or injuries in a patient which comprises **administering** to the site of the disease or injury an effective amount of **at least one serine protease inhibitor** . . . which bind[s] with the mast cells or their mediators." '951 abstract (emphasis added). "The serine protease inhibitors include[] . . . **alpha 1-antitrypsin**. . . . " '951 patent, col. 3, lines 51 - 52 (emphasis added). The serine protease inhibitor may be recombinant, '951 patent, col. 3, line 58, and thus free of admixture with other serine proteases, as are found in plasma-derived products such as PROLASTIN.[6]

The preamble of claim 1 recites that the claimed method is "for treating optic and otic infections, inflammation and kalligrein activity by parasites and microbes."

---

[6] The '951 patent specifically claims use of recombinant AAT. '951 claim 2.

[redacted]

It is beyond debate that the otic infection treated in '951 Example III is caused by "microbes."[7]

As for the paired "inflammation and kalligrein[8]" limitations in the preamble of claim 1, the phrase does not appear in the claim as filed. The phrase was added during prosecution in response to rejection under 35 U.S.C. § 103 over U.S. Pat. No. 5,604,201, which discloses a new AAT mutein having inhibitory specificity for furin endoprotease. The amendatory phrase was intended to clarify that the protease inhibitors to be administered in the methods of the instant patent "form[] complexes to reduce inflammation and pain," which "[t]he variants of native alpha 1-antitrypsin [as disclosed in the cited reference] are not known to form[,] [as] . . . seen from the reference." Amendment filed June 26, 2000 (Paper No. 6), at 3.

Although the arguments proffered by the then-applicants in support of the amendment appear logically infirm and factually unsupported,[9] the import of the

---

[7] Absent an explicit definition by the patentee, the terms used in the claims bear a "heavy presumption" that they have the ordinary meaning that would be attributed by persons skilled in the relevant art, with dictionaries providing a "meaningful source" of information about such meanings. *Texas Digital Sys., Inc. v. Telegenix, Inc.*, 308 F.3d 1193, 64 USPQ2d 1812 (Fed. Cir. 2002). A microbe is "[a] microorganism, especially a bacterium that causes disease; a minute life form. No longer in technical use," The American Heritage® Dictionary of the English Language, 4th Ed (2000).

[8] "Kalligrein", added by amendment filed June 26, 2000 (Paper No. 6), is an unknown, undefined, and thus indefinite term, likely a misspelling of "kallikrein"; appropriate correction should be required. 35 U.S.C. § 112, ¶ 2.

[9] Although the reference cited by the Examiner, U.S. Pat. No. 5,604,201 (filed herewith) discloses that native AAT does not appreciably inhibit furin endoprotease, it neither discloses nor implies the converse, that the AAT Portland mutein, which can inhibit furin endoprotease, no longer binds kallikrein. And factual support for the patentee's assertions that "[t]he protease inhibitors [intended for use in the method of claim 1, such as AAT] function by binding with IgE to prevent the degranulation of mast cells," and that "[a]lpha-1 antitrypsin . . . also complexes with kinins" are, at best, elusive.

amendment itself is clear, making explicit the inherent binding specificity, and thus inhibitory activity, of the protease inhibitors that are to be used in the claimed method.

Each of the three species of protease inhibitor set forth in the body of the claim -- AAT, secretory leukocyte protease inhibitor, and anti-plasmin inhibitor -- necessarily possesses such binding specificity, else the claim would be internally contradictory, including within the Markush group of permissible proteases one or more that fails to satisfy the language of the preamble.

And as the then-applicants note, "[a]lpha-1 antitrypsin. . . complexes with kinins and kallikreins." Amendment filed June 26, 2000 (Paper No. 6), at 3.

Accordingly, the administration of AAT to treat otitis infection, as exemplified in the '951 patent, necessarily anticipates this element of claim 1.

In addition, the '951 patent explicitly teaches methods of treating inflammation and reducing kallikrein activity using protease inhibitors such as AAT:

> The present invention relates to a method for treating . . . inflammatory conditions in patients by the administration of serine protease inhibitors. . . alone or in combination with one or more other serine protease inhibitors which have a specific activity for mast cells or the proteases derived therefrom such as cathepsin-G, elastase, human mast cell chymase, kinins[10] or their precursors. . . .[11]
>
> The serine protease inhibitors which are contemplated in the present invention . . . bind with any one or more of . . . elastase, cathepsin-G, tryptase, chymase, kinins, ***kallikrein***, tumor necrosis

---

[10] The characterization of kinins as proteases appears to be a recurring misapprehension of the inventor/prosecuting attorney, John Lezdey, appearing in a number of his issued patents. Lezdey patents that are made of record in this Request, that are believed to be pertinent but are not relied upon, are listed and briefly summarized at the end of this Request. Copies are enclosed herewith.

[11] '951 col. 2 lines 58 - 65.

factor, chymotrypsin, collagenase, and the like.[12]

U.S. Pat. No. 5,217,951, issued June 8, 1993, discloses each of the elements and limitations of claim 1. Claim 1 is thus invalid under 35 U.S.C. § § 102(a), 102(b) and 102(e) over the '951 patent.

Claim 2 of the instant patent depends directly from claim 1, further reciting that the protease inhibitor to be used in the method is alpha 1-antitrypsin. Claim 2 is anticipated for the reasons elaborated above, incorporated here by reference.

Claim 5 is drawn to the "method of claim 1 including a steroid."

The '951 patent exemplifies the treatment of ear infections through use of PROLASTIN, "followed by administration of a steroid." '951, col. 6, lines 33 - 35. Claim 5 is thus anticipated.

Claim 7 depends from claim 1, further specifying that the method includes an antimicrobial effective amount of an antibiotic.

The '951 patent discloses that "treatment can be followed with the addition of an appropriate steroid or antibiotic," anticipating claim 7.[13]

Claim 9 is drawn to the method of claim 1, "including controlling kallikrein and kinin activity."

Control of kallikrein activity and kinin activity are inherent properties of AAT and the others of the protease inhibitors set forth with specificity in the body of claim 1, as explained by the then-applicants during prosecution: "[a]lpha-1 antitrypsin . . .

---

[12] '951 col. 3, lines 42 - 29.

[13] The disclosure of adjunctive antibiotic administration, '951 patent, col. 3, lines 38 - 41, is drawn with specificity to treatment of chronic dermatitis, not otitis. If such disclosure is not fully anticipatory of claim 7, claim 7 would, in the alternative, have been obvious over this disclosure, 35 U.S.C. § 103.

complexes with kinins and kallikreins." Amendment filed June 26, 2000 (Paper No. 6), at 3.

Claim 9 is thus anticipated by the '951 patent for the reasons set forth with respect to claims 1 and 2, above, incorporated here by reference.

Claim 10 is drawn to "the method of claim 1 including a bradykinin antagonist."

Bradykinin is a nonapeptide (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg) produced by activation of the kinin system in a variety of inflammatory conditions: it is produced, *inter alia*, by the action of plasma kallikrein on high-molecular-weight kininogen, and is destroyed by several kininases in the lungs and other tissues.

The specification neither defines nor provides written description of a "bradykinin antagonist". Absent an explicit disclaimer or clear disavowal, such as by "words or expression of manifest exclusion or restriction," the broad term "bradykinin inhibitor" assumes its plain, ordinary, and broad meaning as any compound that can reduce or inhibit the activity of bradykinin, including compounds that interfere with kallikrein activity; the language of claim 1 is "inimical to any narrower construction." *Housey Pharmaceuticals, Inc. v. AstraZeneca UK Ltd.*, 366 F.3d 1348, 70 USPQ2d 1641 (Fed. Cir. 2004) (construing "an inhibitor or activator of a protein" broadly to include both substances that bind directly to the protein and those that act indirectly elsewhere in the pathway of which the protein is a part).

As discussed above, AAT inhibits kallikrein; such inhibition, in turn, reduces the formation of bradykinin. AAT is thus an antagonist of bradykinin, and claim 10 is therefore anticipated by the '951 patent for the reasons set forth with respect to claims 1 and 2, above.

In summary, claims 1, 2, 5, 7, 9 and 10 are anticipated under 35 U.S.C. §§ 102(a), 102(b) and 102(e) by Lezdey *et al.*, U.S. Pat. No. 5,217,951, issued June 8, 1993, which discloses each element and limitation of these claims.

Anticipation being the epitome of obviousness, *In re Fracalossi*, 681 F.2d 792, 794, 215 USPQ 569, 571 (CCPA 1982); *Connell v. Sears Roebuck & Co.*, 722 F.2d 1542, 1548, 220 USPQ 193, 198 (Fed. Cir. 1983), claims 1, 2, 5, 7, 9 and 10 would also have been obvious under 35 U.S.C. § 103 over the '951 patent.

Claims 1, 2, 5, 7, 9 and 10 would additionally have been obvious over the '951 patent taken in view of Avidano *et al.*, "Analysis of protease activity in human otitis media," *Otolaryngology - Head and Neck Surgery*, 119(4):246 - 351 (October 1998).

Avidano *et al.*, "Analysis of protease activity in human otitis media," *Otolaryngology - Head and Neck Surgery*, 119(4):246 - 351 (October 1998) ("Avidano") follows upon earlier work by other groups in which "serine protease inhibitors α_1-AT and α_2-macroglobulin were identified as acute phase reactants in chinchilla middle ear effusions and were proposed to decrease mucosal damage through the formation of protease-inhibitor complexes." Avidano, p. 350, col. 1.

Using samples suctioned from the ears of 20 human patients with chronic otitis media and otorrhea (discharge), Avidano measured the protease activity present in spontaneous human disease and the effect on that activity of two exogenously added protease inhibitors, alpha-1-antitrypsin and the matrix metalloprotease inhibitor, ilomastat (galardin).

Cultures revealed *Pseudomonas aeruginosa* in samples from 17 of 20 patients; protease activity was detected in 15 of the samples. "Analyzing the 10 samples with the highest protease activity, a statistically significant decrease in activity was seen with ilomastat or α_1-antitrypsin alone and with both ilomastat and α_1-antitrypsin together." Avidano, abstract. The reference concludes, based on the *in vitro* tests, that

"[p]rotease inhibitors effectively decrease protease activity in most cases. . . . " Avidano, abstract.

"The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art." *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988).

The Lezdey '951 patent provides motivation to treat otic infection topically with alpha-1-antitrypsin, teaching the use of recombinant AAT and exemplifying the use of AAT in admixture with small amounts of other serine protease inhibitors that copurify from human plasma. Avidano provides both the motivation to treat otic infection with AAT and a reasonable expectation that AAT can alone significantly reduce protease activity in human otitis. Accordingly, claims 1, 2, 5, 7, 9 and 10 would have been obvious over the '951 patent in view of Avidano.

Claim 16 is independent. Drawn to a composition, the claim recites as follows:

> 16. A composition for ophthalmologic or otolaryngologic application for patients suffering from parasitic infestation or infections characterized by the presence of pseudomonas and increased kallikrein and kinin activity which comprises:
>
> A) about 0 to 20 mg. per milliliter of a protease inhibitor selected from the group consisting of alpha 1-antitrypsin, secretory leucocyte protease inhibitor and anti-plasmin inhibitor;
>
> B) about 0 to 1.5 percent by weight of a steroidal antiphlogistic compound;
>
> C) about 0 to 5 percent by weight of a non-steroidal antiphlogistic compound;
>
> D) about 0 to 1.5 percent of hyaluronic acid, in an aqueous pharmaceutically acceptable base.

The body of claim 16 lists four components of the claimed composition: a protease inhibitor at a concentration of about 0 to 20 mg/ml ("A"); a steroidal

[redacted]

"antiphlogistic" [14] compound present to about 0 to 1.5 percent by weight ("B"); a non-steroidal "antiphlogistic" compound present to about 0 to 5 percent by weight ("C"); and hyaluronic acid ("D") present to about 0 to about 1.5% by weight, composited in an aqueous pharmaceutically acceptable base.

Curiously, all four of components A, B, C, and D can simultaneously be present in the claimed composition in a concentration or amount of "about 0".

The transition is open.

The scope of the claim is, accordingly, unbounded: no particular component is required; additional components may be added, so long as the composition is suitable "for ophthalmalogic[15] or otolaryngologic application."[16] The claim as drafted

---

[14] "Phlogiston" is "a hypothetical substance once believed to be present in all combustible materials and to be released during burning." www.cogsci.princeton.edu/cgi-bin/webwn. The hypothesis has since been rejected. See, *e.g.*, Conant, The Overthrow Of The Phlogiston Theory; The Chemical Revolution Of 1775-1789, Harvard University Press (Cambridge, MA), 1950, Library of Congress call number QD14.C77.

"Antiphlogistic" is therefore an archaic form of "anti-inflammatory."

[15] Properly, "ophthalmølogic". Correction should be required. 35 U.S.C. § 112, ¶ 2.

[16] Although not necessary to dispose of claim 16, it should be noted that the preamble would appear to be nonlimiting.

"If the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction." MPEP § 2111.02 (8th ed., rev. 2), citing *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165 (Fed. Cir. 1999); *Rowe v. Dror*, 112 F.3d 473, 478, 42 USPQ2d 1550, 1553 (Fed. Cir. 1997) ("where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention, the preamble is not a claim limitation"), and others. "If a prior art structure is capable of performing the intended use as recited in the preamble, then it meets the claim." MPEP § 2111.02, citing *In re Schreiber*, 128 F.3d 1473, 1477, 44 USPQ2d 1429, 1431 (Fed. Cir. 1997).

reads on an infinitude of compositions in the prior art, including water ("an aqueous pharmaceutically acceptable base") and a myriad of commercially available solutions for administration to eye or ear. The claim is invalid under 35 U.S.C. §§ 102, 103, and 112, ¶ 2. To the extent that the claim reads on products of nature, the claim is invalid additionally under 35 U.S.C. § 101.

Charitably construing the claim reasonably to require that the composition comprise a nonzero amount[17] of a protease inhibitor selected from the group consisting of alpha 1-antitrypsin, secretory leucocyte protease inhibitor and anti-plasmin inhibitor, the composition is anticipated by the PROLASTIN compositions disclosed in the '951 patent.

To the extent that the nonzero amount must be less than about 20 mg/ml and the '951 patent does not explicitly disclose a composition with sufficient exactitude to be counted an anticipation, such claim would nonetheless have been obvious over the '951 disclosure: the '951 patent motivates the search for an efficacious range of protease inhibitor to be included within the pharmaceutical composition; the routine nature of such dose-finding studies provides a reasonable expectation of successfully finding such range.

In addition or in the alternative, claim 16 would have been obvious over the '951 patent in view of Avidano which, by teaching an *in vitro* assay for measuring the effect of exogenously administered inhibitors on protease activity present in human ear infection, provides a reasonable expectation that a minimally efficacious dose can readily be found.

The body of claim 16 fully sets forth all of the limitations of the composition, defining a structurally complete composition; the preamble of claim 16 should be held to be nonlimiting.

[17] Any amendment of the stated ranges must, however, comply with the written description requirement of the first paragraph of 35 U.S.C. § 112.

B. Claims 1, 5, 9 and 16 are anticipated under 35 U.S.C. §§ 102(a), 102(b), and 102(e) by, and under 35 U.S.C. § 103 would have been obvious over, Lezdey *et al.*, U.S. Pat. No. 5,290,762, issued March 1, 1994, which was not previously of record.

Claims 1, 5, 9 and 16 are anticipated under 35 U.S.C. §§ 102(a), 102(b), and 102(e) by Lezdey *et al.*, U.S. Pat. No. 5,290,762, issued March 1, 1994 ("the '762 patent"). The '762 patent, of which the inventor-prosecutor of the instant patent is both an inventor and the prosecuting attorney, was not made of record during prosecution of the instant patent.

Claims 1, 5, and 9 are described above. It suffices here additionally to note that the protease inhibitor in the method of claim 1 is "selected from the group consisting of alpha 1-antitrypsin, **secretory leucocyte protease inhibitor**, **anti-plasmin inhibitor** and a combination thereof."[18]

The '762 patent, entitled "Treatment of Inflammation," describes "a method for the prophylaxis or direct treatment of inflammatory diseases . . . in a patient which comprises administering to the site of the disease . . . an effective amount of at least one serine protease inhibitor . . . which bind[s] with . . . mast cell mediators, T-cell mediators or kallikrein." '762 patent, abstract. "**The serine protease inhibitors** which are **contemplated** in the present invention are any of the inhibitors, their analogs, derivatives or salts which **can inhibit** mast cell mediators or bind with any one or more of the protease[s] derived from eosinophils, basophils and/or neutrophils such as elastase, cathepsin-G, tryptase, chymase, **kinins**, **kal[l]ikrein**, tumor necrosis factor, chymotrypsin, collagenase, and the like." '762 patent, col. 3, lines 19 - 26 (emphasis added). The '762 patent also claims such methods, with '762 claim 1 reciting:

---

[18] Emphasis added.

1. A method for the treatment of inflammatory diseases or injury in mammals which comprises administering to the site of the disease or injury an effective amount of at least one natural or recombinant serine protease inhibitor selected from the group consisting of **secretory leucocyte protease inhibitor**, . . . **alpha 2-antiplasmin** . . . which has an affinity to a mast cell mediator, plasma kinins or a T-cell mediator.

with claim 6 drawn specifically to:

6. The method of claim 1 wherein said inflammatory disease is **optic or otic**.

The otic inflammatory diseases specifically exemplified in the specification are "ear **infections**,"[19] with administration of the serine protease inhibitor to the ear "followed by the administration of a **steroid**."[20]

Meeting all of the limitations of claims 1, 5, and 9 of the patent for which reexamination is here requested, the '762 patent anticipates these claims under 35 U.S.C. §§ 102(a), 102(b) and 102(e). Anticipation being the ultimate of obviousness, claims 1, 5 and 9 would also have been obvious under 35 U.S.C. § 103 over the '762 patent.

The '762 patent describes and claims pharmaceutical compositions comprising serine protease inhibitors. Claim 15 reads (with emphasis added) as follows:

15. A **pharmaceutical composition** for treatment of a mast cell implicated disease in mammals comprising **an effective amount of at least one natural or recombinant serine protease inhibitor** selected from the group consisting of **secretory leucocyte protease inhibitor**, C-reactive protein, serum amyloid A protein, alpha 2-macroglobulin, **alpha 2-antiplasmin**, its analog, salt or derivative which has an **affinity to** a mast cell mediator, plasma **kinins** or a T-cell mediator, **and a pharmaceutically acceptable carrier**.

---

[19] '762 patent, col. 5, lines 66 - 68.

[20] '762 patent, col. 5, lines 67 - 68.

To the extent that claim 16 of the instant patent can be construed in harmony with the mandates of 35 U.S.C. § 101, 112 first, and 112, ¶2, the claim is directly anticipated by claim 15 of the earlier '762 patent; needless to say, claim 15 forms part of the disclosure of the '762 patent. Anticipated by the '762 patent, claim 16 necessarily would have been obvious thereover.

C. Claims 1, 2, 9, 10 and 16 are anticipated under 35 U.S.C. §§ 102(a), 102(b) and 102(e) by, and under 35 U.S.C. § 103 would have been obvious over, Lezdey *et al.*, U.S. Pat. No. 5,008,242.

Claims 1, 2, 9, 10 and 16 are anticipated under 35 U.S.C. §§ 102(a), 102(b), and 102(e) by Lezdey *et al.*, U.S. Pat. No. 5,008,242, issued April 16, 1991 ("the '242 patent"). The '242 patent, of which the inventor-prosecuting attorney of the instant patent is both an inventor and the prosecuting attorney, was not made of record during prosecution of the instant patent.

The '242 patent discloses treatment of inflammation, specifically optic and otic inflammation, notably inflammation caused by infection, using alpha-1-antichymotrypsin ("AAC"), alone or in combination with alpha-1-antitrypsin.

> Among the . . . **inflammatory** conditions which may . . . be treated are **optic and otic inflammatory conditions**. Such conditions include those associated with conjunctival and corneal injuries including corneal abrasions, blepharitis, conjunctivitis, external otiti[s], inflammation of the ty[m]panic membrane, and the like. The use of alpha 1-antichymotrypsin has been especially useful in the treatment of the various inflammatory conditions of the eyes and ears **including those which are induced by** virus and **bacterial infections**.[21]

---

[21] '242 patent, col. 2, lines 12 - 22 (emphasis added).

> The compound may be used alone or **in combination with** other serine protease inhibitors to provide a broad spectrum of treatment. Preferably, **alpha 1-antitrypsin** is utilized.[22]
>
> If desired, in lieu of alpha 1-antichymotrypsin as the active principal, there may [be] utilized the combination of alpha 1-antichymotrypsin and alpha 1-antitrypsin.[23]

As discussed at some length above, claim 1 of the patent for which reexamination is here requested reads on the therapeutic administration of AAT in admixture with other agents, such as AAC. As elaborated above, and as properly admitted by the patentee during prosecution, AAT necessarily has the anti-inflammatory, kallikrein-inhibitory, and kinin-inhibitory activity required by claim 1.

The '242 patent's disclosure of the therapeutic administration of an AAT:AAC mixture for treatment of otic and optic infections thus directly anticipates claims 1, 2, 9 and 10 of the instant patent. Anticipation being the ultimate of obviousness, claims 1, 2, 9 and 10 would additionally have been obvious over the '242 patent.

Analogously, claim 16, drawn to any pharmaceutical composition comprising AAT, is anticipated and would have been obvious over the disclosure of the '242 patent.

D. Claims 3 and 12 would have been obvious over Lezdey *et al.*, U.S. Pat. No. 5,008,242.

Claim 3 depends directly from claim 1, described above, further limiting the "infection"-causing "microbes" to "pseudomonas." Claim 12 is independent:

---

[22] '242 patent, col. 3, lines 15 - 18 (emphasis added).

12. A method for treating otic infection characterized by elevated pseudomonas and kallikrein activity which comprises administering alpha 1-antitrypsin to the site of infection in a suitable pharmaceutical carrier.

The '242 patent, described in some detail above, particularly discloses that otic solutions comprising alpha-1-antitrypsin in admixture with alpha-1-antichymotrypsin "can be used in the treatment of . . . ***'swimmer's ear'***."[24] "Swimmer's ear" is a lay term for otitis externa, "often caused by infection with *Pseudomonas aeruginosa*."[25]

Although swimmer's ear is "often caused" by *Pseudomonas*, the bacterium is not invariably, or "necessarily", present. Accordingly, inherent anticipation of claims 3 and 12 by the '242 patent might, perhaps, not be found. *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). But with the majority of cases of swimmer's ear associated with *Pseudomonas* infection, claims 3 and 12 would undoubtedly have been obvious over the '242 disclosure, the '242 patent providing both the motivation for, and reasonable expectation of success in, treating such cases of swimmer's ear with an otic solution comprising AAT and AAC.

---

[23] '242 patent, col. 6, lines 23 - 25 (emphasis added).

[24] '242 patent, Example IV, col. 5, lines 38 - 48 (emphasis added).

[25] "Swimmer's Ear" (Otitis Externa). Fact Sheet for Swimmers, Centers for Disease Control and Prevention (CDC), enclosed herewith.

[redacted]

E. Claims 3, 7, 8, 12 and 13 would have been obvious over either or both of Lezdey *et al.*, U.S. Pat. No. 5,008,242 and Lezdey *et al.*, U.S. Pat. No. 5,217,951, in view of Avidano *et al.*, "Analysis of protease activity in human otitis media," *Otolaryngology - Head and Neck Surgery*, 119(4):246 - 351 (October 1998).

Claims 3 and 12, described in detail above, are drawn, *inter alia*, to methods of treating *Pseudomonas* ear infections by the administration of an effective amount of a protease inhibitor, with claim 3 permitting administration of any one or more of alpha 1-antitrypsin, secretory leucocyte protease inhibitor and anti-plasmin inhibitor and claim 12 drawn with specificity to the administration of alpha 1-antitrypsin.[26] Claim 7 is drawn to "[t]he method of claim 1 including an antimicrobial effective amount of an antibiotic", claim 8 to the method of claim 7, "wherein said antibiotic is anti-pseudomonasis."[27] Claim 13 depends from claim 12, wherein "the method of claim 12 include[es] an antibiotic".

Lezdey *et al.*, U.S. Pat. No. 5,008,242, described in detail above, discloses treatment of inflammation, specifically otic inflammation, notably swimmer's ear, using alpha-1-antichymotrypsin ("AAC"), alone or in combination with alpha-1-antitrypsin. It does not explicitly disclose *Pseudomonas* as the causative "microbe" in "swimmer's ear", nor does it describe the adjunctive use of antibiotic therapy in treating otic infection.

---

[26] As with claim 1, claim 12 uses an open transition, thus permitting treatment with the identified protease in admixture with other agents, including other actives.

[27] "Antipseudomonasis" is an unknown term, not present on any of the 4,285,199,774 web pages indexed on the GOOGLE search engine as of September 4, 2004. Nor does the term, used as query, retrieve any of the "over 15 million citations for biomedical articles back to the 1950's" present as of September 4, 2004 on PubMed, a service of the National Library of Medicine (www.ncbi.nlm.nih.gov/pubmed). The term is undefined in the specification, and is thus indefinite. 35 U.S.C. § 112, ¶ 2. For present purposes, it is here interpreted as referring to any antibiotic with efficacy against *Pseudomonas* spp., particularly *aeruginosa*.

Lezdey *et al.*, U.S. Pat. No. 5,217,951, further described above, exemplifies the treatment of otic infection with a composition comprising PROLASTIN, a preparation of α_1-antitrypsin prepared from pooled human plasma. The '951 patent further teaches that the serine protease inhibitor to be administered therapeutically may be recombinant, and thus free of the plasma-derived contaminants found in PROLASTIN. The '951 patent neither mentions nor implies the presence of *Pseudomonas* in ear infections. It does not teach the adjunctive use of antibiotics in treating otic infection.[28]

Avidano *et al.*, "Analysis of protease activity in human otitis media," *Otolaryngology - Head and Neck Surgery*, 119(4):246 - 351 (October 1998) ("Avidano") follows upon earlier work by other groups in which "serine protease inhibitors α_1-AT and α_2-macroglobulin were identified as acute phase reactants in chinchilla middle ear effusions and were proposed to decrease mucosal damage through the formation of protease-inhibitor complexes." Avidano, p. 350, col. 1.

Using samples suctioned from the ears of 20 human patients with chronic otitis media and otorrhea (discharge), Avidano measured the protease activity present in spontaneous human disease and the effect on that activity of two protease inhibitors, alpha-1-antitrypsin and the matrix metalloprotease inhibitor, ilomastat (galardin).

Cultures revealed *Pseudomonas aeruginosa* in samples from 17 of 20 patients. Protease activity was detected in 15 of the samples. "Analyzing the 10 samples with the highest protease activity, a statistically significant decrease in activity was seen with ilomastat or α_1-antitrypsin alone and with both ilomastat and α_1-antitrypsin together." Avidano, abstract. The reference concludes, based on the *in vitro* tests, that "[p]rotease inhibitors effectively decrease protease activity in most cases and in addition

---

[28] That said, the '951 patent teaches that antibiotics may be used in conjunction with serine protease inhibitors in treatment of chronic dermatitis.

to standard antibiotic therapy might prove beneficial in treatment of otitis media with a nonintact tympanic membrane." Avidano, abstract.

Each of the primary Lezdey references, the '951 and '242 patents, alone provides motivation to treat bacterial infection of the ear with alpha-1-antitrypsin, with the '242 patent further specifically motivating such treatment of swimmer's ear. Avidano provides specific motivation to undertake such treatment in otitis caused by, or associated with, the presence of *Pseudomonas aeruginosa*. Having shown that AAT is capable of significantly decreasing protease activity *in vitro*, Avidano provides a reasonable expectation that such treatment will be successful. Claims 3 and 12 of the instant patent would, accordingly, have been obvious over such disclosure. *In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir. 1988).

And by further suggesting that protease administration be conducted "*in addition to* standard antibiotic therapy," Avidano -- alone, and/or in combination with either or both of the primary references -- renders claims 7, 8 and 13 obvious under 35 U.S.C. § 103.

F. Claim 6 would have been obvious under 35 U.S.C. § 103 over either or both of Lezdey *et al.*, U.S. Pat. No. 5,217,951 and Lezdey *et al.*, U.S. Pat. No. 5,290,762, in view of either or both of Lezdey *et al.*, U.S. Pat. No. 5,190,917 and Lezdey *et al.*, U.S. Pat. No. 5,215,965.

Claim 6 would have been obvious over either or both of the '951 patent and '762 patent in view of either or both of Lezdey *et al.*, U.S. Pat. No. 5,190,917, issued March 2, 1993 and Lezdey *et al.*, U.S. Pat. No. 5,215,965, issued June 1, 1993. All four of these patents include, as both an inventor and prosecuting attorney, the inventor-prosecutor of the patent here under consideration; not one of the four was cited by way of information disclosure statement during prosecution of the instant patent.

[redacted]

As discussed at length above, each of the '951 and '762 patents independently anticipates claim 5 of the instant patent, drawn to "[t]he method of claim 1 including a steroid": each discloses the adjunctive use of steroids in the treatment of otic inflammation with serine protease inhibitors, particularly alpha-1-antitrypsin ('951 patent), secretory leucocyte protease inhibitor ('762 patent) and alpha 2-antiplasmin ('762 patent).

Claim 6 depends from claim 5, further specifying that "said steroids are selected from the group consisting of dexamethasone, betametasone[29] and triamcinolone acetonide."

Neither the '951 patent nor the '762 patent specifically recites dexamethasone, betamethasone, or triamcinolone acetonide.

Lezdey *et al.*, U.S. Patent No. 5,190,917, "Treatment of Psoriasis," ("the '917 patent") discloses compositions of serine protease inhibitors, such as alpha-1-antitrypsin, alone or in combination with other serine protease inhibitors, for treatment of psoriasis. The therapeutic compositions can include one or more corticosteroids suitable for topical administration, including **triamcinolone acetonide**, flurandrenolide, prednisone, amcinonide, **dexamethasone**, **betamethasone** valerate, halocinonide, clocortolone, hydrocortisone valerate, and the like. '917 patent, col. 2, line 66 - col. 3, line 2.

Lezdey *et al.*, U.S. Pat. No. 5,215,965 ("the '965 patent"), discloses compositions of serine protease inhibitors, such as alpha-1-antitrypsin, alone or in combination for treatment of mast cell implicated pulmonary diseases. The therapeutic compositions can include one or more corticosteroids selected from the group consisting of **triamcinolone acetonide**, fluorandrenolide, prednisone, amcinonide, beclomethasone

---

[29] "Betametasone", present in claim 6 as filed, is here understood to be a misspelling of "betamethasone"; appropriate correction should be required. 35 U.S.C. § 112, ¶ 2.

[redacted]

valerate, **dexamethasone**, **betamethasone** valerate, halocinonide, clocortolone, hydrocortisone valerate, and the like. '965 Col. 3, lines 63 - 68.

It would have been obvious to select, as the steroid to be used in the methods taught in the Lezdey *et al.* '951 and '762 patents, one or more of the steroids that are commonly used in topical formulations, and that had additionally been disclosed to be effective in admixture or conjunction with a serine protease inhibitor, such as those set forth in the Lezdey *et al.* '917 and '965 patents. The motivation to select a steroid inheres in the teaching of the primary references to use a steroid; the reasonable expectation of success can be inferred from the continued efficacy of the named steroids in admixture or in conjunction with serine protease inhibitors, as taught in the '917 and '965 patents.

Accordingly, claim 6 would have been obvious over either or both of the primary references, taken in view of either or both of the secondary references.

G. Claim 6 would have been obvious under 35 U.S.C. § 103 over either or both of Lezdey *et al.*, U.S. Pat. No. 5,217,951 and Lezdey *et al.*, U.S. Pat. No. 5,290,762 in view of any one or more of U.S. Pat. Nos. 5,061,729; 5,679,665; 4,474,751, and 5,631,241.

Claim 6 would have been obvious over either or both of Lezdey *et al.* '951 patent and Lezdey *et al.* '762 patent in view of any one or more of U.S. Pat. Nos. 5,061,729; 5,679,665; 4,474,751; 5,631,241, or 4,025,620, respectively issued October 29, 1991, October 21, 1997, October 2, 1984, May 20, 1997, and May 24, 1997, none of which have previously been made of record.

The primary references have been described above.

Each of the secondary patent references discloses the selection of one or more of triamcinolone acetonide, dexamethasone, and betamethasone for use in therapeutic compositions intended for otic and/or ophthalmic use.

U.S. Pat. No. 5,061,729 discloses an ear drop composition for the treatment of chronic otitis media which comprises, *inter alia*, a therapeutically effective amount of an antibacterial agent and a therapeutically effective amount of an anti-inflammatory agent selected from the group consisting of hydrocortisone, mazipredone, beclomethasone dipropionate, **triamcinolone acetonide**, prednisolone, **dexamethasone**, and **betamethasone**, or a pharmaceutically acceptable salt thereof.

U.S. Pat. No. 5,679,665 discloses pharmaceutical formulations for ophthalmic and otic topical use that comprise polymyxintrimethoprim (an antibacterial agent) and an anti-inflammatory agent, including, in particular, **dexamethasone**.

U.S. Pat. No. 4,474,751 discloses an aqueous pharmaceutical composition for ophthalmologic use comprising anti-inflammatory drugs selected from the group consisting of hydrocortisone acetate, cortisone, hydrocortisone, **betamethasone**, **dexamethasone**, fluocortolone, prednisolone, methyl prednisolone, medrysone, fluorometholone, prednisolone sodium phosphate, triamcinolone, indomethacin, sulindac and its salts and corresponding sulfide.

U.S. Pat. No. 5,631,241 discloses use of **dexamethasone**, **betamethasone**, and **triamcinolone** in pharmaceutical ophthalmic formulations (with hyaluronic acid derivatives).

U.S. Pat. No. 4,025,620 discloses a drug composition suitable for treatment of otitis in canines, and notes that agents commercially available at the time of filing in the mid-70s included **triamcinolone**.

It would have been obvious to select, as the steroid to be used in the methods taught in the Lezdey *et al.* '951 and '762 patents, one or more of the steroids that are commonly used in topical formulations, and that had additionally been disclosed to be effective specifically for otic or ophthalmologic use, as disclosed in each of the secondary references. The motivation to select a steroid inheres in the teaching of the primary

[redacted]

references to use a steroid; the reasonable expectation of success is found in the efficacy of the pharmaceutical formulations set forth in the secondary references.

Accordingly, claim 6 would have been obvious over either or both of the primary references taken in view of any one or more of the secondary references.

H. Claims 4 and 14 would have been obvious over any one or more of Lezdey *et al.* U.S. Pat. Nos. 5,217,951; 5,290,762; and 5,008,242, in view of either or both of Forney *et al.*, "Anticryptosporidial potential of alpha-1-antitrypsin," *J. Eurkaryot. Microbiol.* 43(5):63S and Forney *et al.*, "Synergistic anticryptosporidial potential of the combination of alpha-1-antitrypsin and paromomycin," *Antimicrobial Agents Chemother.*, Sept. 1997, p. 2006 - 2008.

Claim 4 depends directly from claim 1, limiting claim 1's method for treating "optic and otic infections, inflammation and kalligrein [*sic*] activity" to treatment of "parasites . . . selected from the group consisting of Shistosoma mansoni[30] and cryptosporidium parvum." Claim 14 is independent, and recites:

> 14. A method for treating optic and otic infestation by parasites which comprises administering an effective amount of alpha 1-antitrypsin to the site of infestation inflammation and kallikrein activity in a suitable pharmaceutical carrier.

The limitation "inflammation and kallikrein" was added to claim 14 by amendment concurrently with, and for the same reasons as, the amendment of claim 1; its construction should therefore be identical.

Lezdey *et al.* U.S. Patent Nos. 5,217,951; 5,290,762, and 5,008,242, above-described, disclose treatment of otic and/or optic inflammation, including infections, with various of the proteases set forth in claim 1 of the Lezdey *et al.* patent for which

---

[30] The correct spelling is *Schistosoma mansoni*; correction should be required under 35 U.S.C. § 112, 2nd paragraph.

reexamination is here requested. The Lezdey *et al.* references do not mention cryptosporidia.

Forney *et al.*, "Anticryptosporidial potential of alpha-1-antitrypsin," *J. Eurkaryot. Microbiol.* 43(5):63S (Sept-Oct 1996) and Forney *et al.*, "Synergistic anticryptosporidial potential of the combination of alpha-1-antitrypsin and paromomycin, "*Antimicrobial Agents Chemother.*, Sept. 1997, p. 2006 - 2008, disclose the anticryptosporidial potential of alpha-1-antitrypsin, when used alone or in combination with an antibiotic. The Forney references do not mention otitis.

It would have been obvious to treat those cases of otitis caused by cryptosporidium parvum with alpha-1-antitrypsin: the Lezdey patents motivate treatment of any type of otic inflammation; the Forney references provide a reasonable expectation of successfully so treating cases caused by cryptosporidia. Cryptosporidium parvum is a parasite within the scope of claim 14.

Accordingly, claims 4 and 14 are invalid under 35 U.S.C. § 103.

[redacted]

III. Prior Art Newly Made Of Record And Considered Pertinent To Patentee's Claims, But Not Relied Upon in this Request, 37 C.F.R. § 1.501(a).

- **Lezdey *et al.*, U.S. Patent No. 5,114,917, "Treatment of inflammation using alpha 1-antichymotrypsin," issued May 19, 1992.**

Lezdey *et al.*, U.S. Patent No. 5,114,917 is a continuation-in-part of Lezdey *et al.*, U.S. Patent No. 5,008,242 and anticipates claims 1, 2, 9 and 16 for the same reasons. Like the '242 patent, Lezdey *et al.*, U.S. Patent No. 5,114,917, includes as inventor and prosecuting attorney the inventor-prosecutor of the Lezdey *et al.* patent for which reexamination is here requested; like the '242 patent, it was not previously made of record.

Each of the following patents is also considered pertinent to patentee's claims: each may be combined under 35 U.S.C. § 103 with one or more of the references over which reexamination is here requested. Each includes, in the dual role as inventor and prosecuting attorney, the inventor-prosecutor of the instant patent; none was made of record during prosecution of patent for which reexamination is here requested.

- **Lezdey *et al.*, U.S. Patent No. 5,346,886, "Topical α-1-antitrypsin, non-aqueous lipid miscible, benzalkonium chloride compositions for treating skin," issued September 13, 1994.**

Lezdey *et al.*, U.S. Patent No. 5,346,886 discloses pharmaceutical preparations containing serine protease inhibitors for use in topical applications. Particularly disclosed are serine protease inhibitors that bind with kallikrein, including alpha-1-antitrypsin. The reference further discloses combination of serine protease inhibitors with a corticosteroid.

- **Lezdey *et al.*, U.S. Patent No. 5,166,134, "Treatment of Allergic Rhinitis," issued November 24, 1992.**

Lezdey *et al.*, U.S. Patent No. 5,166,134, discloses nasal administration of a serine protease inhibitor which inhibits mast cells or binds with their mediators, including alpha-1-antitrypsin. The reference further notes that "Alpha 1-antitrypsin has . . . been found especially useful because of its association with . . . kinins." Col. 3, lines 36 - 40. "In accordance with one method of treatment, 0.1% to 2.5% by weight of a solution such as a serine protease inhibitor, particularly α1-antitrypsin, alone or in combination with other serine protease inhibitors such as a1-antichymotrypsin, in a sterile water or saline solution, may be used by the patient as a nose drop or nasal spray." Col. 4, lines 9 - 16.

- **Lezdey *et al.*, U.S. Patent No. 5,492,889, "Treatment of Mast Cell Tumors," issued February 20, 1996.**

Lezdey *et al.*, U.S. Patent No. 5,492,889, discloses methods for treating tumors in mammals by the administration of alpha 1-antitrypsin alone or in combination with other protease inhibitors. The reference further discloses coadministration with a steroid.

- **Lezdey *et al.*, U.S. Patent No. 5,093,316, "Treatment of Inflammation," issued March 3, 1992**

Lezdey *et al.*, U.S. Patent No. 5,093,316, discloses topical, aerosol treatment of pulmonary inflammation with microcrystalline alpha-1-antitrypsin, alone or in combination with other serine protease inhibitors, such as alpha-1-antichymotrypsin and C-reactive protein.

- **Lezdey *et al.*, U.S. Patent No. 5,134,119, "Treatment of Inflammation Using 358 Substituted Alpha-Antitrypsin," issued July 28, 1992**

Lezdey *et al.*, U.S. Patent No. 5,134,199, discloses treatment of mast-cell implicated inflammatory diseases, notably dermatological, with α-1-antitrypsin having an aliphatic residue substituted to methionine at 358. Diseases proposed to be treated include inflammatory skin diseases, including those induced by virus and bacterial infections, preferably with increased IgE levels showing an allergic condition.

- **Lezdey *et al.*, U.S. Patent No. 5,532,215, "Antiviral Compositions and Method of Use," issued July 2, 1996.**

Lezdey *et al.*, U.S. Patent No. 5,532,215, discloses use of serine protease inhibitors, including AAT and secretory leukocyte protease inhibitor, in systemic and topical treatment of viral infections.

- **Lezdey *et al.*, "Treatment of Pulmonary Disease with Protease Inhibitors," U.S. Pat. No. 5,780,440, issued July 14, 1998.**

Lezdey *et al.*, U.S. Patent No. 5,780,440, discloses treatment of respiratory distress syndrome and/or sepsis by administration into the lungs of at least one protease inhibitor, alone or with an oxygen metabolite scavenger. Preferred protease inhibitors include alpha 1-antitrypsin and secretory leucocyte protease inhibitor, alone or in combination.

[redacted]

CONCLUSION

The undersigned third party requests *ex parte* reexamination of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14 and 16 of U.S. Patent No. 6,174,859, which are respectfully submitted to be invalid under one or both of 35 U.S.C. §§ 102 and 103 over prior art not previously made of record.

Respectfully submitted,

HELLER EHRMAN WHITE & MCAULIFFE LLP

Date: September 22, 2004

Ginger R. Dreger (Reg. No. 33,055)

Date: 22 SEPTEMBER 2004

Daniel M. Becker (Reg. No. 38,376)

275 Middlefield Road
Menlo Park, CA 94025
(650) 324-7000
(650) 324-0638 (FAX)
Customer No. 25213

3-21-05

Third Party Requester Docket No.: 39042.0005

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Reexam control no.:	90/007,215		
Confirm. No.:	9354	Examiner:	Phyllis G. Spivack
Patent No.:	6,174,859	Group Art Unit.:	1614
Patentee:	LEZDEY *et al.*		
Filed:	April 6, 1999		
For:	METHOD OF TREATMENT		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY UNDER 37 C.F.R. § 1.535

Sir:

In response to the Patent Owner's Statement under 37 C.F.R. § 1.530, timely served by deposit in first class mail on January 20, 2005, the undersigned Third Party Requester ("requester") submits the following reply under 37 C.F.R. § 1.535. The requester files concurrently herewith:

- a supplemental Information Disclosure Statement ("IDS"), with a copy of each cited reference; and
- a certificate of service, certifying service of this paper and its accompanying IDS on the attorney of record for the patent owner, pursuant to 37 C.F.R. § 1.248.

REMARKS

The order for reexamination of U.S. Patent No. 6,174,859 (the "instant patent") finds that each of the eight (8) contentions set forth in the Third Party Request for *Ex Parte* Reexamination ("reexam request") separately and independently raises a substantial new question of patentability affecting claims of the instant patent. In a timely filed statement under 37 C.F.R. § 1.530, the patent owner offers the following rejoinder, reproduced here in its entirety:[1]

> Patent owner will file a Declaration swearing back of the publication date of the Avidano et al article.
>
> Also, Patent owner will submit scientific publications which illustrate that there is a distinction in treating bacterial disease from mast cell or viral disease.

Neither the promised Declaration nor the promised scientific publications have since been filed.

This Reply thus addresses both of the Patent Owner's unsupported contentions in necessarily general terms.[2] Having failed to abide by the rule that "[a]ny statement filed by the patent owner ***shall clearly point out*** why the subject matter as claimed is not anticipated or rendered obvious by the prior art patents or printed publications," 37 C.F.R. § 1.530(c) (emphasis added), the Patent Owner should not now be heard to complain that the requester's comments range across the entire territory thus opened for exploration.

---

[1] The Patent Owner Statement under 37 C.F.R. § 1.530 proposes no amendments.

[2] In the interests of brevity, the comments do not touch on all of the invalidity contentions set forth in detail in the reexam request; to the extent not here discussed, however, those contentions are hereby explicitly reaffirmed and incorporated herein by reference in their entireties.

In addition, this Reply presents further substantial new questions of patentability over art not previously made of record.[3]

I. The "Distinction" Intended To Be "Illustrated" Is Irrelevant To Each Of The Eight (8) Substantial New Questions Of Patentability

A. The promised (and as yet undocumented) "distinction" can negate neither anticipation of claims 1, 2, 5, 7, 9, 10 and 16 by Lezdey *et al.*, U.S. Pat. No. 5,217,951, nor the obviousness of the claims thereover

Claim 1 of the instant patent is independent, and recites as follows:

> 1. A method for treating optic and otic infections, inflammation and kalli[k]rein activity by parasites and microbes which comprises administering to the site of the infection an effective amount of a protease inhibitor selected from the group consisting of alpha 1-antitrypsin, secretory leucocyte protease inhibitor, anti-plasmin inhibitor and a combination thereof in a suitable pharmaceutically acceptable carrier.

As described in detail in the reexam request, the specification of the '951 patent exemplifies the treatment of "ear infections" by administration of an "otic wash" solution comprising PROLASTIN, a sterile preparation of α_1-antitrypsin ("AAT") prepared from pooled human plasma of normal donors.[4]

As a purely definitional matter, "[i]nfections" are caused by infectious agents. Although the causative infectious agents are not specifically identified in Example III of the '951 patent, they are assuredly microscopic; they are, to revisit an old

---

[3] "The reply need not be limited to the issues raised in the statement. The reply may include additional prior art patents and printed publications and may raise any issue appropriate for reexamination." M.P.E.P. § 2251 (8th ed., 2nd rev.).

term, "microbes."[5] As discussed at length in the reexam request, AAT necessarily and inherently possesses the anti-inflammatory and kallikrein inhibitory activity required by claim 1 of the instant patent. Disclosing each and every element and limitation of claim 1, Example III of the '951 patent fully anticipates the claim, and alone would have rendered it obvious.

In response, the patent owner will allegedly produce "scientific publications which illustrate that there is a distinction in treating bacterial disease from mast cell or viral disease."[6]

---

[4] '951 patent, Example III, col. 6, lines 21 - 36, particularly at lines 21 - 25 and 33 - 35.

[5] Indeed, "[e]ar infections are generally characterized by the presence of pseudomonas." U.S. Pat. No. 6,174,859 (the instant patent) at col. 3, lines 13 - 14. *Pseudomonas* is a genus of bacteria -- that is to say, a genus of microorganisms, of *"microbes"*.

[6] The discussion that follows assumes, for sake of argument, that the Patent Owner will, as alleged, in due course illustrate that there is a "distinction in treating bacterial disease from mast cell . . . disease". This Reply demonstrates that the claims under reexamination are invalid notwithstanding any such alleged "distinction".

In truth, however, the alleged "distinction" is rather more indistinct than the Patent Owner might hope: "[m]ast cells are not only important in IgE-associated disorders but also contribute to host defense against bacteria." Galli *et al.*, "Mast cells to the defense," *Nature Immunology* 4:1160-1162 (2003).

> Mast cells, historically known for their involvement in type I hypersensitivity, also serve critical protective and homeostatic functions. They directly recognize the products of bacterial infection through several surface receptor proteins releasing proteases, cytokines, and eicosanoid mediators that recruit neutrophils, limit the spread of bacterial infection, and facilitate subsequent tissue repair.

Boyce, "Mast cells: Beyond IgE," *J. Allergy Clin. Immunol.* 111:24 -32 (2003).

As early as 1997, it was known for example that "mast cells recognize and react to a wide range of microorganisms or their products . . . lend[ing] . . . credence to the notion that mast cells have the potential to markedly influence the course of microbial infections"; the data further supported the notion "that the raison d'être for the mast cell is initiating and coordinating the host's inflammatory and immune responses against microbial pathogens." Abraham *et al.*, "Minireview: Mast Cells in Infection and Immunity," *Infection & Immunity* 65:3501-3508 (September 1997), at p. 3501, col. 1 (filed herewith).

The promised references are as yet undisclosed, their disclosures as yet unknown.

Whatever they may ultimately turn out to be, however, they will not turn out to be relevant: example III of the '951 patent meets each and every element and limitation of, and thus anticipates, claim 1 of the instant patent, and will continue to do so -- the "ear infections" treated with AAT in the prior art '951 patent will not suddenly and retroactively be sterilized by a later-illustrated "distinction" between treating "bacterial disease" and "mast cell [disease]".

Whatever "distinction" may ultimately be shown between treating "bacterial disease", on the one hand, and "mast cell [disease]", on the other, in the end that distinction cannot transform the purely semantic difference between the "ear infections" in the '951 patent and the "otic infections" caused by "microbes" in claim 1 of the instant patent into a patentable distinction.

Equally, and for the same reason, the promised publications cannot and will not negate anticipation of claims 2, 5, 7, 9, 10 and 16 of the instant patent by the '951 disclosure on the grounds set forth in detail in the reexam request, nor render those claims nonobvious thereover.

B. The promised "distinction" -- currently unsupported -- can negate neither anticipation of claims 1, 5, 9 and 16 by Lezdey *et al.*, U.S. Pat. No. 5,290,762, nor the obviousness of the claims thereover

As described in greater detail in the reexam request, the '762 patent claims (and thus describes, 35 U.S.C. § 112, ¶ 1):

> 1. A method for the treatment of inflammatory diseases or injury in mammals which comprises administering to the site of the disease or injury an effective amount of at least one natural or recombinant serine protease inhibitor selected from the group consisting of **secretory**

leucocyte protease inhibitor, . . . **alpha 2-antiplasmin** . . . which has an affinity to a mast cell mediator, plasma kinins or a T-cell mediator.

6. The method of claim 1 **wherein said inflammatory disease is** optic or **otic**.

Although otic inflammation is not invariably caused by, or necessarily accompanied by, infection, the '762 "examples further illustrate the practice of th[e] ['762] invention"[7]; the otic inflammatory diseases specifically exemplified are "ear **infections**."[8]

Once present in the prior art, "ear infections" remain in the prior art. They do not become other than microbial infections, even by the later production of references that will allegedly illustrate a "distinction" between treating "bacterial disease" and "mast cell [disease]". The "microbes" remain, as does anticipation, and thus the obviousness, of claim 1. So too, for the reasons first advanced in the reexam request, anticipation and obviousness of claims 5, 9 and 16.

C. The promised, but as yet unsupported, "distinction" cannot negate anticipation of claims 1, 2, 9, 10 and 16 by Lezdey *et al.*, U.S. Pat. No. 5,008,242, and thus cannot negate the obviousness of the claims thereover

The '242 patent discloses treatment of inflammation, specifically optic and otic inflammation, notably inflammation caused by bacterial infection, using alpha-1-antichymotrypsin ("AAC"), alone or in combination with AAT.

Among the . . . **inflammatory** conditions which may . . . be treated are **optic and otic inflammatory conditions**. Such conditions include those associated with conjunctival and corneal injuries including corneal abrasions, blepharitis, conjunctivitis, external otiti[s], inflammation of the

---

[7] '762 patent, col. 5, lines 14 - 15.

[8] '762 patent, Example III, col. 5, lines 66 - 68 (emphasis added).

ty[m]panic membrane, and the like. The use of alpha 1-antichymotrypsin has been especially useful in the treatment of the various inflammatory conditions of the eyes and ears **including those which are induced by** virus and **bacterial infections**.[9]

The compound may be used alone or **in combination with** other serine protease inhibitors to provide a broad spectrum of treatment. Preferably, **alpha 1-antitrypsin** is utilized.[10, 11]

If desired, in lieu of alpha 1-antichymotrypsin as the active principal, there may [be] utilized the combination of alpha 1-antichymotrypsin and alpha 1-antitrypsin.[12]

The patent owner intends to produce "scientific publications which illustrate that there is a distinction in treating bacterial disease from mast cell or viral disease." Those publications, and that illustration, cannot act retrospectively to elide the words "bacterial infections" from printed prior art. Claims 1, 2, 9, 10 and 16 remain anticipated, and thus obvious, over the '242 patent.

D. Claims 3 and 12 of the instant patent remain obvious over Lezdey *et al.*, U.S. Pat. No. 5,008,242, notwithstanding an alleged, but as yet unproven, "distinction" "in treating bacterial disease from mast cell or viral disease"

Claim 3 of the instant patent depends directly from claim 1, further limiting the "infection"-causing "microbes" to "pseudomonas." Claim 12 is independent:

12. A method for treating otic infection characterized by elevated pseudomonas and kallikrein activity which comprises

---

[9] '242 patent, col. 2, lines 12 - 22 (emphasis added).

[10] '242 patent, col. 3, lines 15 - 18 (emphasis added).

[11] As described in detail in the reexam request, claim 1 of the instant patent reads on administration of AAT in combination with other actives.

[12] '242 patent, col. 6, lines 23 - 25 (emphasis added).

administering alpha 1-antitrypsin to the site of infection in a suitable pharmaceutical carrier.

By the patent owner's own admission, "[e]ar infections are generally characterized by the presence of pseudomonas,"[13] and on this admission alone claims 3 and 12 of the instant patent should be found to have been obvious over any one or more of the Lezdey '951, '762 , and '242 patents.[14] The '242 patent additionally discloses that otic solutions comprising alpha-1-antitrypsin in admixture with alpha-1-antichymotrypsin "can be used in the treatment of . . . 'swimmer's ear'."[15] As detailed in the reexam request, "swimmer's ear" is a lay term for otitis externa, often caused by infection with *Pseudomonas aeruginosa.*

The patent owner may yet illustrate a "distinction" between treating bacterial and mast cell diseases. But the distinction that the patentee **needs** to prove is a distinction between the *Pseudomonas* in the prior art and *Pseudomonas* in claims 3 and 12 of the instant patent. With such proof not likely forthcoming, claims 3 and 12 will continue to be obvious over the '242 patent[16] for the reasons of record.

---

[13] U.S. Pat. No. 6,174,859 (the instant patent) at col. 3, lines 13 - 14.

[14] "In rejecting claims the examiner may rely upon admissions by the . . . patent owner in a reexamination proceeding, as to any matter affecting patentability. . . . " 37 CFR § 1.104(c)(3). Indeed, "[t]o ignore an admission by the patent owner, from any source, and not use the admission as part of the prior art in conjunction with patents and printed publications in reexamination would make it impossible for the examiner to properly determine the scope and content of the prior art. . . . " M.P.E.P. § 2258 (8th ed., rev. 2).

[15] '242 patent, Example IV, col. 5, lines 38 - 48.

[16] And indeed, over the '951 and '762 patents as well.

E. The references that are alleged to be forthcoming cannot of themselves vitiate the obviousness of claims 3, 7, 8, 12 and 13 over either or both of the '242 and '951 patents, further in view of Avidano

Claims 3 and 12 of the instant patent are drawn, *inter alia*, to methods of treating *Pseudomonas* ear infections by the administration of an effective amount of a protease inhibitor. Claim 7 is drawn to "[t]he method of claim 1 including an antimicrobial effective amount of an antibiotic", claim 8 to the method of claim 7, "wherein said antibiotic is anti-pseudomonasis."[17] Claim 13 depends from claim 12, wherein "the method of claim 12 includ[es] an antibiotic".

As set forth in detail in the reexam request, and briefly touched on above, each of the primary references, the Lezdey '951 and Lezdey '242 patents, explicitly teaches that microbial infections of the ear can be treated effectively with alpha 1-antitrypsin. *A fortiori*, each provides *motivation* to treat bacterial infection of the ear with AAT, with the '242 patent further specifically motivating such treatment of "swimmer's ear". Avidano, in turn, provides specific motivation to undertake such treatment in otitis caused by, or associated with, the presence of *Pseudomonas aeruginosa*. Having shown that AAT is capable of significantly decreasing *Pseudomonas*-associated protease activity *in vitro*, Avidano additionally provides a reasonable expectation that such treatment will be successful.

Nothing in the Patent Owner's references -- promised to "illustrate that there is a distinction in treating bacterial disease from mast cell or viral disease" -- would change the teachings of the primary references or alter the experimental results reported

---

[17] The reexam request notes that the term "antipseudomonasis", undefined in the specification of the instant patent, could not be found on any of the 4,285,199,774 web pages indexed on the GOOGLE search engine as of September 4, 2004.

Despite the near doubling of web pages indexed on the GOOGLE search engine since that time (8,058,044,651 web pages as of March 16, 2005), the term "antipseudomonasis" (and, equally, the hyphenate, "anti-pseudomonasis") remains unknown.

in Avidano. The Patent Owner's references cannot, of themselves, save the claims from invalidation as having been obvious over the '951 and/or '242 patent in view of Avidano.[18]

F. The Patent Owner's alleged "distinction" -- even if ultimately, albeit untimely, illustrated -- has no bearing on the selection of the steroids specifically recited in claim 6

As discussed in detail in the reexam request, each of the '951 and '762 patents independently anticipates claim 5 of the instant patent, drawn to "[t]he method of claim 1 including a steroid": each discloses the use of steroids as an adjunct to treatment of ear infections with serine protease inhibitors, specifically as an adjunct to treatment with alpha 1-antitrypsin ('951 patent), secretory leucocyte protease inhibitor ('762 patent) and alpha 2-antiplasmin ('762 patent). Claim 6 depends from claim 5, further specifying that "said steroids are selected from the group consisting of dexamethasone, betametasone[19] and triamcinolone acetonide."

Neither the '951 patent nor the '762 patent specifically recites dexamethasone, betamethasone, or triamcinolone acetonide, three well-known corticosteroids oft-used in topical formulation.[20]

Lezdey *et al.*, U.S. Pat. No. 5,190,917, and Lezdey *et al.*, U.S. Pat. No. 5,215,965, each disclose that one or more of the three corticosteroids named in the

---

[18] The Patent Owner's assertion that he will antedate the Avidano reference is separately addressed in part II of this Reply.

[19] "Betameth*a*sone" is presumed.

[20] See, *e.g.*, the lists of FDA-approved pharmaceutical products containing the named steroids, both current and discontinued, downloaded from the FDA's electronic Orange Book, and filed herewith.

Markush group of claim 6 is effective in admixture or in conjunction with a serine protease inhibitor.

Each of U.S. Pat. Nos. 5,061,729; 5,679,665; 4,474,751; 5,631,241, and 4,025,620 discloses the selection of one or more of triamcinolone acetonide, dexamethasone, and betamethasone for use in therapeutic compositions intended for otic and/or ophthalmic use.

As discussed in the reexam request, it would have been obvious to select, as the steroid to be used in the methods of treating otic infection taught in the Lezdey *et al.* '951 and '762 patents, one or more of the steroids that are commonly used in topical formulations, and that had additionally been disclosed to be effective in admixture or conjunction with a serine protease inhibitor, such as those set forth in the Lezdey *et al.* '917 and '965 patents. The motivation to select a steroid inheres in the teaching of the primary references to use a steroid; the reasonable expectation of success can be inferred from the continued efficacy of the named steroids in admixture or in conjunction with serine protease inhibitors, as taught in the '917 and '965 patents.

It would additionally have been obvious to select, as the steroid to be used in the methods taught in the Lezdey *et al.* '951 and '762 patents, one or more of the steroids that are commonly used in topical formulations, and that had additionally been disclosed to be effective specifically for otic or ophthalmologic use, as disclosed in U.S. Pat. Nos. 5,061,729; 5,679,665; 4,474,751; 5,631,241, and 4,025,620 . The motivation to select a steroid inheres in the teaching of the primary references to use a steroid; the reasonable expectation of success is found in the efficacy of the pharmaceutical formulations set forth in the secondary references.

Whatever the Patent Owner's references may ultimately disclose, they will not disclose any datum, any theory, any conclusion that can reach back through time to remove the three corticosteroids named in claim 6 of the instant patent from the earlier-existing clinical armamentarium, that can undo the disclosure of the inventor's own

earlier patent disclosures, or that can erase the disclosures of the five prior art third party patents that disclose the selection of one or more of triamcinolone acetonide, dexamethasone, and betamethasone for use in therapeutic compositions intended for otic and/or ophthalmic use. Claim 6 would have been, and will remain, obvious.

G. A later-demonstrated "distinction" between "bacterial diseases" and "mast cell" diseases neither robs AAT of its "anticryptosporidial potential" nor attenuates the "synergistic anticryptosporidial potential of the combination of alpha-1-antitrypsin and paromomycin"

Claim 4 depends directly from claim 1, limiting claim 1's method for treating "optic and otic infections" to treatment of "parasites . . . selected from the group consisting [*inter alia*] of . . . cryptosporidium parvum." Claim 14 is independent, and recites:

> 14. A method for treating optic and otic infestation by parasites which comprises administering an effective amount of alpha 1-antitrypsin to the site of infestation inflammation and kallikrein activity in a suitable pharmaceutical carrier.

Forney *et al.*, "Anticryptosporidial potential of alpha-1-antitrypsin," *J. Eurkaryot. Microbiol.* 43(5):63S (Sept-Oct 1996) and Forney *et al.*, "Synergistic anticryptosporidial potential of the combination of alpha-1-antitrypsin and paromomycin, "*Antimicrobial Agents Chemother.*, Sept. 1997, p. 2006 - 2008, disclose the anticryptosporidial potential of alpha-1-antitrypsin, when used alone or in combination with an antibiotic.

As described at length in the reexam request, and briefly above, Lezdey *et al.* U.S. Patent Nos. 5,217,951; 5,290,762, and 5,008,242 disclose treatment of otic and/or optic inflammation, including infections, with various of the proteases set forth in claim 1 of the instant patent. It would have been obvious to treat those cases of otitis

caused by cryptosporidium parvum with alpha-1-antitrypsin: the Lezdey patents motivate treatment of any type of otic inflammation; the Forney references provide a reasonable expectation of successfully so treating cases caused by cryptosporidia.

Nothing in the Patent Owner's expected proffer can change these facts. Claims 4 and 14 of the instant would have been obvious under 35 U.S.C. § 103, and after the Patent Owner's production of "publications", claims 4 and 14 will remain so.

II. The Promised Declaration, When Ultimately Produced, Cannot Save The Reexamined Claims From Invalidation

A. The Declaration will be completely irrelevant to six (6) of the eight (8) substantial new questions of patentability

The Patent Owner's Statement under 37 C.F.R. § 1.530 asserts that the "Patent owner will file a Declaration swearing back of the publication date of the Avidano et al article."

Six of the eight substantial new questions of patentability do not rely upon the Avidano *et al.* ("Avidano") reference.

Thus, even if the promised Declaration were found to provide a showing of facts that are "such, in character and weight, as to establish reduction to practice" of the invention of each and every one of claims 1, 2, 3, 5, 7, 8, 9, 10, 12, 13 and 16 of the instant patent[21] "prior to the effective date of the [Avidano] reference" , "or conception of the invention" set forth in each and every one of claims 1, 2, 3, 5, 7, 8, 9, 10, 12, 13 and 16 "prior to the effective date of the reference coupled with due diligence from prior to said date to a subsequent reduction to practice or to the filing of the application,"

---

[21] The claims that would otherwise have been obvious over Avidano.

37 C.F.R. § 1.131(b) -- and even if the declaration were thus found sufficient to remove Avidano as prior art with respect to these claims -- the following six grounds for invalidating the claims here under reexamination would, perforce, remain undisturbed:

2. Claims 1, 5, 9 and 16 are anticipated under 35 U.S.C. §§ 102(a), 102(b), and 102(e) by, and under 35 U.S.C. § 103 would have been obvious over, Lezdey *et al.*, U.S. Pat. No. 5,290,762, not previously made of record.

3. Claims 1, 2, 9, 10 and 16 are anticipated under 35 U.S.C. §§ 102(a), 102(b) and 102(e) by, and under 35 U.S.C. § 103 would have been obvious over, Lezdey *et al.*, U.S. Pat. No. 5,008,242, not previously made of record.

4. Claims 3 and 12 would have been obvious under 35 U.S.C. § 103 over Lezdey *et al.*, U.S. Pat. No. 5,008,242, not previously made of record.

6. Claim 6 would have been obvious under 35 U.S.C. § 103 over either or both of Lezdey *et al.*, U.S. Pat. No. 5,217,951 and Lezdey *et al.*, U.S. Pat. No. 5,290,762 in view of either or both of Lezdey *et al.*, U.S. Pat. No. 5,190,917 and Lezdey *et al.*, U.S. Pat. No. 5,215,965, none of which have previously been made of record.

7. Claim 6 would have been obvious under 35 U.S.C. § 103 over either or both of Lezdey *et al.*, U.S. Pat. No. 5,217,951 and Lezdey *et al.*, U.S. Pat. No. 5,290,762 in view of any one or more of U.S. Pat. Nos. 5,061,729; 5,679,665; 4,474,751; 5,631,241; or 4,025,620, none of which have previously been made of record.

8. Claims 4 and 14 would have been obvious under 35 U.S.C. § 103 over either or both of Forney *et al.*, "Anticryptosporidial potential of alpha-1-antitrypsin," *J. Eukaryot. Microbiol.* 43(5):63S and Forney *et al.*, "Synergistic anticryptosporidial potential of the combination of alpha-1-antitrypsin and paromomycin," *Antimicrobial Agents Chemother.*, Sept. 1997, p. 2006 - 2008 in view of any one or more of Lezdey *et al.* U.S. Pat. Nos. 5,217,951; 5,290,762; and 5,008,242, none of which have previously been made of record.

B. The promised Declaration will be equally inapplicable to two of the alternatives presented in another of the substantial new questions of patentability

As set forth in detail in the reexam request, claims 1, 2, 5, 7, 9, 10 and 16 are (i) anticipated under 35 U.S.C. §§ 102(a), 102(b) and 102(e) by Lezdey *et al.*, U.S. Pat. No. 5,217,951, (ii) under 35 U.S.C. § 103 would have been obvious thereover, and (iii) under 35 U.S.C. § 103 would have been obvious thereover, further in view of Avidano.

Although presented as a single contention in the reexam request, only the last of the three alternative grounds would be affected by an effective Declaration under 37 C.F.R. § 1.131; the other two remain undisturbed, and each continues to present a sufficient basis to invalidate claims 1, 2, 5, 7, 9, 10 and 16.

III. Art Not Previously Made Of Record Raises Additional Substantial New Questions Of Patentability

A. Claim 11 would have been obvious under 35 U.S.C. § 103 over any one or more of Lezdey *et al.* U.S. Pat. Nos. 5,217,951; 5,290,762; and 5,008,242, in view of U.S. Pat. No. 5,166,331, not previously made of record

Claim 11 of the instant patent depends directly from claim 1, further "including hyaluronic acid" in claim 1's "method for treating optic and otic infections, inflammation and kalli[k]rein activity by parasites and microbes", the method comprising "administering to the site of the infection an effective amount of a protease inhibitor. . . ."

As demonstrated at length in the reexam request, claim 1 is separately anticipated by each of U.S. Pat. Nos. 5,217,951, 5,290,762 and 5,008,242, and would be

anticipated by any combination thereof. None of these primary references describes the use of hyaluronic acid in ophthalmic or otic formulations.

U.S. Pat. No. 5,166,331 ("the '331 patent"), issued November 24, 1992 and thus available under 35 U.S.C. § 102(b) as against the claims of the instant patent, describes fractions of hyaluronic acid that are useful, *inter alia*, "to provide ophthalmic solutions having excellent toleration to the cornea."[22]

> On the basis of the results [reported in the patent] . . . , it can be concluded that solutions of hyaluronic acid sodium salt (in both the HYALASTINE and HYALECTIN fractions) can be used as a vehicle for ophthalmic drugs and proves to be efficient as such for various types of drugs having differing biological actions. For example, drugs including anti-glaucoma agents such as pilocarpine nitrate, anti-allergic and anti-inflammatory agents such as triamcinolone, tissue healing and cell proliferation promoting agents for promoting healing of eye tissue such as EGF, and antibiotics such as streptomycin and gentamicin[], whose miotic, anti-inflammatory, healing and antimicrobial activities are reported, can all be administered effectively utilizing HA [hyaluronic acid] as a vehicle.
>
> The formulations of ophthalmic drugs vehicled in hyaluronic acid fractions with various molecular weights prove to be perfectly tolerated by the host, and compatible with the corneal epithelium without, therefore, giving rise to sensitization phenomena.
>
> It is also possible from the data to observe how this biological product, hyaluronic acid, is an efficient vehicle, capable of enhancing the in vivo bioavailability of vehicled drugs, strengthening the pharmacological activity of such drugs. . . .
>
> The results obtained by using this biological polymer, hyaluronic acid, as a vehicle for drugs with such varied natures and actions, allows of the extrapolation of its potential as a vehicle for numerous other ophthalmic drugs.[23]

---

[22] U.S. Pat. No. 5,166,331, col. 2, lines 66 - 68.

[23] U.S. Pat. No. 5,166,331, col. 44, line 54 - col. 45, line 31.

The '331 patent explicitly teaches the advantages of using hyaluronic acid ("HA") as a vehicle for ophthalmic delivery of a wide variety of drugs, including both anti-inflammatory agents and therapeutic proteins, and explicitly and literally suggests that the use of hyaluronic acid as an ophthalmic vehicle be "extrapola[ted]" to other drugs. The '331 patent provides the suggestion and motivation to include HA with the anti-inflammatory protease inhibitor proteins in the ophthalmic treatment methods of the '951, '762, and '242 patents, and further provides a reasonable expectation of successfully so doing. Claim 11 would, therefore, have been obvious over any one or more of U.S. Pat. Nos. 5,217,951; 5,290,762; and 5,008,242, in combination with the '331 disclosure.

B. Claim 15 would have been obvious under 35 U.S.C. § 103 over either or both of Forney *et al.*, "Anticryptosporidial potential of alpha-1-antitrypsin," *J. Eukaryot. Microbiol.* 43(5):63S and Forney *et al.*, "Synergistic anticryptosporidial potential of the combination of alpha-1-antitrypsin and paromomycin," *Antimicrobial Agents Chemother.*, Sept. 1997, p. 2006 - 2008 in view of any one or more of Lezdey *et al.* U.S. Pat. Nos. 5,217,951; 5,290,762; and 5,008,242, further in view of U.S. Pat. No. 5,166,331, not previously made of record

Claim 15 of the instant patent depends directly from claim 14, further "including hyaluronic acid" in claim 14's "method for treating optic and otic infestation by parasites", the method comprising "administering an effective amount of alpha 1-antitrypsin to the site of infestation. . . . "

Lezdey *et al.* U.S. Patent Nos. 5,217,951; 5,290,762, and 5,008,242, disclose treatment of otic and/or optic inflammation, including infections, with various of the proteases set forth in claim 14 of the instant patent. The Lezdey *et al.* references do not mention cryptosporidia.

Forney *et al.*, "Anticryptosporidial potential of alpha-1-antitrypsin," *J. Eurkaryot. Microbiol.* 43(5):63S (Sept-Oct 1996) and Forney *et al.*, "Synergistic

anticryptosporidial potential of the combination of alpha-1-antitrypsin and paromomycin, "*Antimicrobial Agents Chemother.*, Sept. 1997, p. 2006 - 2008, disclose the anticryptosporidial potential of alpha-1-antitrypsin, when used alone or in combination with an antibiotic. The Forney references do not mention otitis.

It would have been obvious to treat those cases of otitis caused by cryptosporidium parvum with alpha-1-antitrypsin: the Lezdey patents motivate treatment of any type of otic inflammation; the Forney references provide a reasonable expectation of successfully so treating cases caused by cryptosporidia. Cryptosporidium parvum is a parasite within the scope of claim 14.

The '331 patent explicitly teaches the advantageous use of hyaluronic acid ("HA") as a vehicle for ophthalmic delivery of a wide variety of drugs, including both anti-inflammatory agents and therapeutic proteins, and explicitly suggests that the use of hyaluronic acid as an ophthalmic vehicle be "extrapola[ted]" to other drugs. The '331 patent provides both ample motivation to include HA with the anti-inflammatory protease inhibitor proteins in such anticryptosporidial treatment methods, and a reasonable expectation of successfully so doing. Claim 15 would, therefore, have been obvious over the above-cited combination.

CONCLUSION

The undersigned third party requester respectfully submits that claims 1 - 16 of U.S. Patent No. 6,174,859 are invalid under one or both of 35 U.S.C. §§ 102 and 103 over the prior art made of record in this reexamination, and respectfully request the issuance of a reexamination certificate canceling the claims.

Respectfully submitted,

HELLER EHRMAN WHITE & McAULIFFE LLP
Third Party Requester

Date: MARCH 18, 2005

Daniel M. Becker (Reg. No. 38,376)

275 Middlefield Road
Menlo Park, CA 94025
(650) 324-7000
(650) 324-0638 (FAX)
Customer No. 25213